SEP 4 1930

VOL. CLXXX, No. 3 SEPTEMBER, 1930 No. 702

Medical Library

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

E. B. KRUMBHAAR, M.D., EDITOR
RICHARD A. KERN, M.D., ASSISTANT EDITOR

ESTABLISHED 1820

OBSERVATIONS ON THE ETIOLOGIC RELATIONSHIP OF ACHYLIA GASTRICA TO PERNICIOUS ANEMIA. III. THE NATURE OF THE REACTION BETWEEN NORMAL HUMAN GASTRIC JUICE AND BEEF MUSCLE LEADING TO CLINICAL IMPROVEMENT AND INCREASED BLOOD FORMATION SIMILAR TO THE EFFECT OF LIVER FEEDING. By WILLIAM B. CASTLE, M.D., WILMOT C. TOWNSEND, M.D., and CLARK W. HEATH, M.D. 305

THE NORMAL FILAMENT AND NONFILAMENT POLYMORPHONUCLEAR NEUTROPHIL COUNT: ITS PRACTICAL VALUE AS A DIAGNOSTIC AID. By DAVID L. FARLEY, M.D., HUSTON ST. CLAIR, M.D., and JOHN A. REISINGER, M.D. 336

NOTE ON THE DIAGNOSIS OF PNEUMOCOCCUS PERITONITIS FROM THE BLOOD PICTURE. By CHARLES L. GIBSON, M.D 344

STUDIES CONCERNING DIGITALIS THERAPY IN LOBAR PNEUMONIA. By WALTER L. NILES, M.D., and JOHN WYCKOFF, M.D. 348

BARIUM CHLORID IN THE STOKES-ADAMS SYNDROME OF COMPLETE HEART BLOCK. NEGATIVE RESULTS IN EIGHT CASES. By AARON E. PARSONNET, M.D., and ALBERT S. HYMAN, M.D. 356

A STUDY OF UNINFECTED MURAL THROMBI OF THE HEART. By EARLE A. HARVEY, M.D., and SAMUEL A. LEVINE, M.D. 365

FLARIMETER TESTS OF CIRCULATORY FITNESS: A PRELIMINARY REPORT. By L. F. MacKENZIE, M.D., P. V. WELLS, D.Sc., E. G. DEWIS, M.D., and L. S. YLVISAKER, M.D. 372

THE PRODUCTION OF HYPERTROPHIC ARTHRITIS BY INTERFERENCE WITH THE BLOOD SUPPLY. By ARTHUR D. GOLDHAFT, V.M.D., LILLIE M. WRIGHT, M.A., and RALPH PEMBERTON, M.D. 386

SUBPHRENIC ABSCESS. By GATEWOOD, M.D. 398

REMOTE SYMPTOMS OF UNRECOGNIZED THYROID ADENOMATA. WITH LOW BASAL METABOLIC RATE RELIEVED BY OPERATION. By P. K. GILMAN, M.D., and W. E. KAY, M.D. 405

ANOREXIA NERVOSA, ANOREXIA, INANITION, AND LOW BASAL METABOLIC RATE. By JOHN M. BERKMAN, M.D. 411

INDEX TO PHYSICIANS' SUPPLIES . . . . . ADV. PAGE 50

Contents continued on page x

OWNERS AND PUBLISHERS
LEA & FEBIGER
PHILADELPHIA

COPYRIGHT, 1930, BY LEA & FEBIGER. ALL RIGHTS RESERVED. ENTERED AT THE POST-OFFICE AT PHILADELPHIA AS SECOND-CLASS MATTER
PUBLISHED MONTHLY. SUBSCRIPTION, SIX DOLLARS A YEAR, POSTPAID

Like MAGIC

In a few days, the boil is gone! Physicians no longer tolerate the painful lance and its danger of spreading deadly infection.

Oral medication with **STANNOXYL** has superseded the lance in modern practice. Gone are the days of the crisscross incision, the irksome dressing and the lifetime scar.

Prescribe 4 to 8 Stannoxyl tablets daily and watch the inflammation and pain subside. Send for sample today.

ANGLO-FRENCH DRUG CO. (U. S. A)., INC.

1270 Broadway, New York

STANNOXYL

There is only one way to find out what STANNOXYL will do . . .

. . . and that is to *try it* in your own practice. Send your request—today—on a prescription blank or postal card, and we will send you a quantity sufficient for full clinical trial.

THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

SEPTEMBER, 1930

ORIGINAL ARTICLES.

OBSERVATIONS ON THE ETIOLOGIC RELATIONSHIP OF ACHYLIA GASTRICA TO PERNICIOUS ANEMIA.*

III. The Nature of the Reaction Between Normal Human Gastric Juice and Beef Muscle Leading to Clinical Improvement and Increased Blood Formation Similar to the Effect of Liver Feeding.†

By William B. Castle, M.D.,

ASSISTANT PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL, AND ASSOCIATE PHYSICIAN, THORNDIKE MEMORIAL LABORATORY, BOSTON CITY HOSPITAL,

Wilmot C. Townsend, M.D.,

FORMERLY ASSISTANT IN TROPICAL MEDICINE, HARVARD MEDICAL SCHOOL; ASSISTANT RESIDENT PHYSICIAN, THORNDIKE MEMORIAL LABORATORY, AND RESIDENT PHYSICIAN, TROPICAL MEDICAL SERVICE, BOSTON CITY HOSPITAL,

AND

Clark W. Heath, M.D.,

ASSISTANT IN MEDICINE AND TROPICAL MEDICINE, HARVARD MEDICAL SCHOOL; ASSISTANT RESIDENT PHYSICIAN, THORNDIKE MEMORIAL LABORATORY, AND RESIDENT PHYSICIAN, TROPICAL MEDICINE SERVICE, BOSTON CITY HOSPITAL.

(From the Thorndike Memorial Laboratory of the Boston City Hospital, and the Department of Medicine, Harvard Medical School.)

It has been demonstrated by the experiments reported in the first two papers of this series[1,2] that the normal human stomach, by virtue of its content of secretions, can produce by an interaction with beef muscle a substance effective in a fashion similar to liver in promoting prompt blood regeneration and clinical improvement in Addisonian pernicious anemia. Since this function of the con-

* An essay containing the subject matter of the two preceding papers of this series (I and II) and of the first section of this paper, by William B. Castle and Wilmot C. Townsend, was awarded the Warren Triennial Prize of the Massachusetts General Hospital for 1928.

† The expenses of the present investigation were borne in part by grants from the J. K. Lilly gift to the Medical School of Harvard University.

tents of the normal stomach was shown to be in contrast to the inability of the patient with pernicious anemia to produce such an effect from ingested beef muscle, a critical analysis of this process becomes essential to a further comprehension of the nature of the disease. The source of the constituent of the gastric contents active in the production of those effects was the liquid removed from the stomachs of healthy fasting subjects during the hour subsequent to the subcutaneous injection of 0.5 mg. of histamin phosphate.[3] The other constituent of the effective reaction as previously described was lean-beef muscle divided as finely as possible with a special meat chopper. In preparing the materials for incubation 200 gm. of the beef muscle were carefully mixed with from 150 to 300 cc. of the fasting gastric contents and brought to a temperature of 37.5° C. while hydrochloric acid (usually from 5 to 10 cc. of a two-thirds concentrated solution) was added until the reaction of the material was just distinctly orange to Töpfer's reagent (pH 2.5 to 3.5). The mixture was then kept in the incubator for two hours with occasional stirring and the addition of a few drops of acid to maintain a relatively constant acidity. The material was then removed from the incubator, passed through a wire strainer and strong sodium hydroxid added until a pH value of 5 was obtained. It was then given daily, usually within half an hour, to the fasting patient by means of a nasal tube introduced into the stomach, and no food was taken by the patient for at least an hour thereafter. It is therefore evident that the process freely permits an interaction between a factor present in the normal gastric juice, which may thus be termed intrinsic, and a factor contained in the beef muscle, which is thus an extrinsic element.

Analysis of the Nature of the Intrinsic Factor. Since the outstanding difference between the digestive tract of the patient with pernicious anemia and that of the normal individual is the inability of the stomach of the former to secrete hydrochloric acid[4] or pepsin,[5] and since the environment, at least in the *in vitro* phase of the conditions under which normal fasting human gastric contents secreted after histamin stimulation have been shown to create the effective substance, is such as to promote peptic digestion, it appeared possible that peptic hydrolysis was the intimate nature of the process leading to the production of the effective agent. However, after the partial neutralization with the sodium hydroxid, and after introduction into the gastrointestinal tract of the patient, a potentially significant *in vivo* phase began, in which opportunity might have been afforded for the saliva or bile occasionally contaminating the gastric juice of the normal individual to interact effectively with the beef muscle or for a different action of the gastric juice upon the beef muscle to take place. The negative experiments with fasting gastric contents alone, obtained after

histamin injection[2] (Cases 11, 19 and 24), indicate no possibility of direct hematopoietic action by any of the constituents of the normal gastric contents, but only of their indirect action upon the beef muscle. It appeared desirable, therefore, to eliminate certain of these possibilities at once by an attempt to reproduce with the use of purer sources of peptic activity the effects seen with fasting normal gastric contents.

A series of experiments will now be described as performed upon cases of classical Addisonian pernicious anemia. The ward diets utilized contained no red meat, liver or kidneys. The blood studies were carried out as already described,[1] and the criteria of activity in promoting blood formation were those clearly defined by Minot and his associates[6,7] and previously shown to be applicable to those experiments.[1] A positive effect was considered to be indicated by a significant response of reticulocytes within ten days after the beginning of the uniform daily administration of the material to be tested. This was always associated with clinical improvement and eventually in most instances by an increase of over 1,000,000 red blood cells per cubic millimeter. Conversely, a negative effect was considered to be indicated by the absence of a significant increase of reticulocytes within a period of ten days. In the tables the data are given for alternate days only during the administration of the test preparations.

(*a*) *The Effect of the Incubation of Beef Muscle with Pepsin in the Presence of Hydrochloric Acid.* Pepsin (U.S.P.) is available in the form of dry, yellowish granules. It is prepared by the autolysis of the mucous membrane of the pig's stomach in the presence of hydrochloric acid,[8] and is actively proteolytic in acid solution. A solution of this substance in dilute hydrochloric acid was therefore used, instead of normal human fasting gastric contents recovered after histamin stimulation, during the incubation of the beef muscle in observations on 3 patients. Two hundred grams of beef muscle were mixed in a beaker with from 100 to 200 cc. of warm tap water in which had been dissolved from 2 to 5 gm. of the pepsin. While the temperature of the mixture was being brought to that of the incubator, strong hydrochloric acid was added until the reaction of the mixture was slightly orange to Töpfer's reagent (pH 2.5 to 3.5). The material was then incubated for from two to twenty-four hours in different experiments, the resulting liquid passed through a wire strainer, neutralized to pH 5 and administered to the fasting patients exactly as was done in the experiments with the gastric juice as a source of peptic activity. Table I shows the results of this therapy in the control periods of the 3 cases so treated (Cases 9, 10 and 21). It will be noted that in none of these patients was there the slightest evidence of an effect on either reticulocytes or the total number of red blood cells, although in the subsequent test

periods of Cases 9 and 10, excellent remissions were induced with the gastric contents of normal individuals recovered after they had ingested beef muscle.[1] In Case No. 21, liver extract given later yielded a satisfactory remission.

In the observations on a fourth case (Case 20) (See Table I) there was conducted for another purpose an even more convincing experiment, since in this case the environment for the activity of the pepsin was actually normal human gastric juice inactivated in terms of these experiments by previous heating to from 70° to 80° C. for a half hour. The endowment of this inactivated gastric juice during the control period with proteolytic ability provided by the pepsin was found to be an unsuccessful substitute for the original essential activity of the unheated gastric juice clearly demonstrable in the subsequent test period. The experiments carried out on 2 other subjects (Cases 23 and 34), designed primarily for other purposes demonstrate incidentally in the control periods the negative action of pepsin and hydrochloric acid, and also in the subsequent test periods its inability to produce an inhibitory effect on the usual action of normal human fasting gastric contents obtained after histamin stimulation. It must be concluded, therefore, from the behavior of these 6 cases, that peptic hydrolysis by means of pig pepsin is incapable of duplicating the results seen with human gastric juice. This at that time somewhat surprising negative result has already been briefly reported[9,10] and has since been confirmed by Wilkinson.[11]

(*b*) *The Effect of the Incubation of Beef Muscle with Normal Human Gastric Juice Rendered Proteolytically Inactive by Heat.* Since an unexpected obstacle to the direct proof of the assumed importance of peptic hydrolysis had been encountered in the failure of the experiments with pig pepsin, it became necessary to attempt to adduce indirect evidence for the possible significance of peptic hydrolysis or a related enzyme process taking place with human gastric juice. If it could be shown that when the enzymes of the gastric juice were rendered inactive the effect was not obtained evidence at least consistent with the idea of an enzyme action would be obtained. Accordingly, the usual technique of *in vitro* incubation of 200 gm. of beef muscle with 150 cc. of human gastric juice was employed, with the exception that the gastric juice was first heated on a water bath for a half hour at a temperature between 70° and 80° C., and then rapidly cooled to 37.5° C. before incubation with the beef muscle. This, as was shown with Mett's tubes, effectively destroyed all peptic activity. However, in order to be certain that the physical aspects of the digestion were carried out, 2 gm. of pepsin were added to the mixture immediately before its incubation. It was, of course, already known from three of the experiments just reported that this substance, though proteolytically active, was incapable of producing the effective principle from

beef muscle. After neutralization to pH 5, the incubated material was given to Case 20 for a period of ten days with the entirely negative result, shown in the control period (Table I). The procedure was now changed during the test period of this patient only by using unheated gastric juice. The pepsin was added in order to be certain that it could not have acted in some way as an inhibitant to the production of the active principle in the procedure of the control period. An excellent remission was promptly obtained, with a maximum production of reticulocytes of 19.6 per cent on the eighth day at an initial level of 2.28* million red blood cells per cubic millimeter, and a gain of over a million red blood cells per cubic millimeter during the eighteen days of this treatment. It is then clear that the heating of the gastric juice was the cause of the failure of any effect to appear in the control period of this case.

Since the peptic activity of the gastric contents was destroyed by heating, the experiment is entirely consistent with the idea of the indispensability of the peptic hydrolysis of protein for the production of the effective substance. Despite the negative effects with pig pepsin it still seemed possible that the negative effect was due to the destruction of the human pepsin, the chief proteolytic enzyme of the human gastric juice, particularly as the chief constituent of the beef muscle used in these experiments was protein. If, however, the action of the human pepsin were assumed to be the basis of the positive effects seen with the fasting gastric contents, the negative effects in the experiments with the pepsin of the pig would have to be explained by a difference in the sources of pepsin. On the other hand, the difference between the action of pig pepsin and of human gastric juice might indicate that the effective intrinsic factor of the latter was not secreted by the human gastric mucosa, and hence was not found in the preparation made from the homologous organ of the pig. It appeared logical, therefore, next to attempt to narrow down the possible sources of the effective substance acting as the intrinsic factor in the positive reactions with human gastric contents. The unavoidable presence of saliva and the occasionally regurgitated duodenal contents in the gastric juice as used made it impossible to be certain that the intrinsic effective substance was secreted by the normal gastric mucosa. The probability that this was so, particularly in view of the well-known clinical pathology of the stomach in pernicious anemia, appeared to be great; but absolute proof was lacking by this use of gastric juice representing secretions other than those of the stomach wall itself.

(*c*) *The Effect of the Incubation of Beef Muscle with Normal Human Saliva.* Accordingly, it was decided first to test the possible rôle of the normal salivary action in these experiments. In order to give an optimum chance for effect of the saliva to display itself,

* For convenience in referring to the tables the red blood cell count of the second day of the test period is taken as the initial figure.

200 gm. of beef muscle were carefully chewed by one or more healthy normal subjects and expectorated into a beaker which was then placed in the incubator for one hour. No change in the physical appearance of the beef muscle occurred during this time. To this material was now added from 150 to 200 cc. of warm tap water, 3 gm. of pepsin and enough strong hydrochloric acid to give a pH of from 2.5 to 3.5. After thorough mixing, the material was incubated for two hours and given daily to Case 23, immediately after neutralization to pH 5. As it was already known from the experiment with heated gastric juice (Case 20) that the pepsin could neither cause nor inhibit an effect if produced by another constituent, this conduct of the control period of the experiment would certainly give the saliva both before and after encountering the acid-pepsin mixture, an opportunity to act presumably even better than that afforded to the swallowed saliva ordinarily present in the gastric contents. In Table I data are presented which show the entirely negative effect of this procedure during the control period of Case 23. A prompt effect appeared during the test period when the only change in the procedure consisted of the substitution of fasting human gastric contents for the water used in the control period. The resulting remission was characterized by a maximum production of reticulocytes on the eighth day of 12.8 per cent, and an increase of the red blood cell count from 1.90 to 3.05 millions per cubic millimeter within twenty days. The pepsin was again shown to have no effect in inhibiting the production of the effective substance, and the salivary activity, even under optimum conditions, was demonstrated to have played no part in the process.

(*d*) *The Effect of the Incubation of Beef Muscle with Normal Human Duodenal Contents.* It now remained to determine whether the small amounts of duodenal secretions occasionally obtained with the fasting gastric contents had been operative in the production of the effective substance. This seemed a remote possibility because of the fact that bile was by no means regularly present in the gastric contents and had been rarely encountered in the contents of the normal stomachs recovered after the ingestion of the beef muscle. Furthermore, the enzymes of the duodenum of patients with pernicious anemia are ordinarily found to be normally active.[12] Since at the acid reactions utilized in the *in vitro* incubations with gastric juice the enzymes of the duodenum could hardly have been active[13,14], the phase of the process in which such activity might have been manifest was presumably that following the administration of the material to the patient subsequent to neutralization to pH 5. It therefore seemed proper to test the effect of the duodenal contents near the neutral point and a reaction of pH 7 was chosen for the *in vitro* incubation and subsequent administration to the patient. This conduct of the experiment was also apparently necessitated by another difficulty inherent in the usual methods available for col-

lecting human duodenal contents, for by means of a simple duodenal intubation it obviously would be impossible to collect duodenal contents completely free from gastric juice. If, then, the incubation were carried out at an acid reaction, it would be impossible to exclude the possibility of the participation of the pepsin of the gastric juice recovered with the duodenal contents. On the other hand, because none of the patients so far had received material at any other acidity than at pH 5, in the event of a negative result it would be necessary to prove subsequently the effectiveness of the products of the incubation of the beef muscle with gastric juice when administered to the patient at the neutral point.

The subjects furnishing the duodenal contents were healthy medical students in the fasting condition. The duodenal contents collected each day from one subject were used that day for one patient in the observations to be described. A duodenal tube was swallowed and the tip allowed to enter the second portion of the duodenum where its position was checked by fluoroscopic examination. The subject was then given about 30 cc. of olive oil by mouth to promote secretion, and the characteristic golden-brown contents of the duodenum collected over a period of about an hour. The material had usually a reaction of about pH 7 or if slightly acid was brought to that point with a little sodium hydroxid and at once placed in the icebox. In this fashion, about 150 cc. of duodenal contents containing a little olive oil were obtained daily. The customary 200 gm. of beef muscle were brought to pH 7 with strong sodium hydroxid and then thoroughly mixed with the duodenal contents at the same pH, while the temperature of the mixture was being brought to 37.5° C. After an incubation period of two hours the material was again brought to pH 7 with a few drops of strong sodium hydroxid, passed through a wire strainer and administered each day to the fasting patient for a period of ten days.

An inspection of the data for Case 28 presented in Table I suggests that an effective interaction took place between the duodenal contents and the beef muscle during the control period, since at the relatively high initial red blood cell level of 2.5 million per cubic millimeter, a maximum production of 5.1 per cent of reticulocytes appeared on the eighth day. In order to determine whether or not this was a maximum effect for this procedure, in the immediately following ten-day test period 200 gm. of beef muscle were incubated in the ordinary manner with 150 cc. of normal gastric juice at pH 2.5 to 3.5 and given daily to the patient after neutralization to pH 5. It will be seen that there was no secondary rise of reticulocytes, a fact which may be taken to indicate that this procedure was incapable of producing detectably more of the effective substance than was the interaction of the duodenal contents and the beef muscle at pH 7. This positive result with duodenal contents appeared so contrary to expectation that the experiment was carried out on

Case 32 in essentially the same way, except that in the test period the beef muscle was first liquefied by incubation with pepsin at pH 2.5 to 3.5 for two hours and then after neutralization to pH 7 was incubated for two hours with gastric juice obtained with great care free from duodenal contents. The material was also administered to the patient at pH 7. As with Case 28, the interaction of the duodenal contents and beef muscle at pH 7 gave evidence of the formation of an effective substance resulting on administration to this patient at an initial red blood cell count of 1.66 million per c.mm. in a maximum production of 12.4 per cent of reticulocytes on the tenth day of the treatment. In the subsequent test period, incubation of the beef muscle with 5 gm. of pepsin at pH 2.5 to 3.5, followed by incubation with fasting gastric juice at pH 7 caused no second rise of reticulocytes and thus gave no indication of a greater production of the effective principle. There was no doubt, therefore, that these normal duodenal contents, containing some gastric juice, even though incubated and administered at a neutral reaction, could produce the effective principle in amounts not detectably less than those produced with gastric juice.

The obvious explanation of this phenomenon, that the reaction was due to the action on the beef muscle of some factor or factors in the duodenal contents other than gastric juice, seemed unsatisfactory because of the known pathologic physiology of the gastrointestinal tract in pernicious anemia. It has been shown that in contrast to the defective enzyme activity of the stomach of these patients,[5] the enzymes of the duodenal contents are ordinarily found to be normally active.[12] Furthermore, the basis of all the effects previously seen with the normal human gastric contents could hardly have been the presence of variable small amounts of regurgitated duodenal contents; and if so, it was difficult to see why the apparently normal duodenal contents of the pernicious anemia patient could not effectively produce from the feeding of beef muscle alone a sufficiency of the effective principle. That this was not possible was clearly demonstrated[1] in the observations during the control Cases 1, 4 and 10. In these early experiments it was shown that between 200 and 300 gm. of finely-divided beef muscle fed daily to patients with pernicious anemia were totally ineffective in terms of these reactions. However, a second possibility was that since the normal duodenal contents contained much bile just derived from the liver of a normal individual, a portion of the liver extract content of that organ might have been excreted with the bile and so be the basis of the effects seen in these particular experiments. This, however, seemed in all probability excluded by the negative effect of the daily administration for ten days of the material resulting from the incubation of 150 cc. of normal duodenal contents with an indifferent protein preparation in the control period of Case 29, shortly to be described. (See Table II.)

TABLE I.—RESULTS OF ADMINISTERING TO 10 CASES OF PERNICIOUS ANEMIA BEEF MUSCLE AFTER INCUBATION WITH THE FOLLOWING: PEPSIN (PIG) AND

TABLE I.—RESULTS OF ADMINISTERING TO 10 CASES OF PERNICIOUS ANEMIA BEEF MUSCLE AFTER INCUBATION WITH THE FOLLOWING: PEPSIN (PIG) AND HCl, NORMAL HUMAN GASTRIC JUICE PREVIOUSLY HEATED, GASTRIC JUICE UNHEATED AT pH 7, NORMAL SALIVA, NORMAL DUODENAL CONTENTS AT pH 7 CONTAINING RESPECTIVELY GASTRIC JUICE AND NO GASTRIC JUICE, AND WITH SMALL AMOUNTS OF FRESH PIG GASTRIC MUCOSA.

Control Periods.

Daily administration of various substances as indicated below.

Days of treatment.	Beef muscle, 200 gm., incubated with pepsin (pig) and HCl.						Beef muscle, 200 gm., incubated with heated gastric juice, pepsin and HCl.		Beef muscle, 200 gm., incubated with saliva, pepsin and HCl.		Beef muscle, 200 gm., incubated with duodenal contents containing gastric juice at pH 7				No control.		Beef muscle, 200 gm., incubated with duodenal contents containing no gastric juice at pH 7.		Beef muscle, 200 gm., incubated with 100 gm. pig's gastric mucosa.	
	Case 9.		Case 10.		Case 21.		Case 20.		Case 23.		Case 28.		Case 32.		Case 33.		Case 34.		Case 36.	
	R.B.C. (mils.).	Retics. (%).	R.B.C. (mils.)	Retics. (%).	R.B.C. (mils.).	Retics. (%).	R.B.C. (mils.).	Retics. (%).	R.B.C. (mils.).	Retics. (%).	R.B.C. (mils.).	Retics. (%).	R.B.C. (mils.).	Retics. (%).	R.B.C. (mils.).	Retics. (%).	R.B.C. (mils.).	Retics. (%).	R.B.C. (mils.).	Retics. (%).
0	1.03	0.1	2.36	2.0	2.65	1.0	2.40	0.8	2.03	1.4	2.50	1.2	1.66	2.7	....	....	1.27	0.8	1.72	0.2
2	0.93	1.1	2.40	0.8	2.88	0.8	2.39	0.8	2.33	1.2	2.59	1.4	1.33	1.6	....	....	1.13	1.7	1.53	0.4
4	0.79	0.3	2.04	1.9	2.88	2.8	2.36	0.4	2.17	0.4	2.74	1.0	1.36	1.2	....	....	1.14	0.8	1.52	0.6
6	0.84	0.9	2.06	1.1	2.84	1.6	2.37	0.6	1.82	0.4	2.96	**5.1**	1.51	5.0	....	....	1.20	2.3	1.46	5.4
8	0.84	0.8	2.08	1.4	2.67	0.6	2.03	0.6	2.12	0.4	2.73	2.8	1.35	7.9	....	....	1.03	**4.8**	1.37	**22.0**
10	1.02	1.1	2.15	1.2	2.75	0.8	1.99	0.2	....	....	2.69	2.4	1.30	**12.4**	....	....	1.08	2.8	1.95	2.5

Test Periods.

Daily administration of various substances as indicated below.

	Contents normal stomach recovered after ingestion 300 gm. beef muscle.				Same as in control period.		Same as in control period except gastric juice unheated.		Same as in control period except with addition gastric juice.		Beef muscle, 200 gm., incubated with gastric juice.				Beef muscle, 200 gm., incubated with pepsin and HCl, then with gastric juice containing no bile at pH 7.				Same as in control period except 25 gm. pig's gastric mucosa.	
2	1.57	0.8	2.61	0.2	2.78	1.6	2.28	0.4	1.90	0.4	2.83	2.2	1.59	6.4	1.43	0.8	1.21	2.3	1.55	0.6
4	1.68	0.6	2.56	0.6	2.62	2.0	2.49	1.2	2.00	1.6	2.89	1.2	1.51	3.6	1.33	1.6	1.14	5.0	1.53	1.6
6	1.24	0.7	2.48	0.8	....	....	2.48	10.8	2.14	5.0	3.21	1.0	1.70	2.9	1.63	10.7	1.28	8.3	1.74	3.6
8	1.33	0.9	2.52	2.8	....	....	2.87	**19.6**	1.85	**12.8**	3.00	1.0	1.81	3.8	1.79	**17.1**	1.30	**28.4**	1.53	**8.6**
10	1.66	4.6	2.68	**6.8**	....	....	3.00	7.6	2.42	9.4	3.30	1.4	2.11	2.2	1.86	3.4	1.81	13.0	1.69	4.8
12	1.53	9.6	2.69	5.5	....	....	2.80	4.8	2.70	9.7	....	....	2.35	0.8	2.56	2.6	2.09	8.8	1.78	3.4
14	1.39	**13.2**	3.00	4.0	....	....	3.28	4.6	2.62	5.6	....	....	....	....	2.66	1.8	1.86	7.3		
16	1.55	8.4	3.00	2.6	....	....	3.75	2.2	2.63	4.0	....	....	....	....	2.77	1.2	2.33	2.8		
18	1.46	8.8	3.33	2.9	Subsequent		3.76	1.2	2.64	5.0	....	....	....	....	2.93	1.2				
20	1.50	6.9	3.58	1.0	good		....	....	3.05	2.8										
22	1.57	3.6			response to															
24	1.84	3.6			liver extract															

TABLE II.—RESULTS OF ADMINISTERING TO 5 CASES OF PERNICIOUS ANEMIA BEEF MUSCLE PROTEIN AFTER INCUBATION WITH NORMAL HUMAN GASTRIC JUICE.

Control Periods.

Daily administration of various substances as indicated below.

Days of treatment.	No control.		No control.		Gluten flour 100 gm. incubated with gastric juice.		Protein from beef muscle 200 gm. incubated with duodenal contents.		No control.	
	CASE 25.		CASE 26.		CASE 27.		CASE 29.		CASE 35.	
	R.B.C. (mils.).	Retics. (%).	R.B.C. (mils.).	Retics. (%).	R.B.C. (mils.).	Retics. (%).	R.B.C. (mils.).	Retics. (%).	R.B.C. (mils.).	Retics. (%).
0	....	....	....	....	1.33	1.8	1.37	0.6	....	....
2	....	....	....	....	1.46	1.6	1.26	0.6	....	....
4	....	....	....	....	1.13	1.4	1.14	1.4	....	....
6	....	....	....	....	1.21	1.3	1.20	2.3	....	....
8	....	....	....	....	1.16	1.2	1.29	2.1	....	....
10	....	....	....	....	1.28	1.8	....	....	....	....

Test Periods.

Daily administration of substances as indicated below.

	Protein free of fat and carbohydrate precipitated at PH 6 from 200 gm. beef muscle incubated with gastric juice.									
2	1.31	2.6	1.81	1.2	1.01	1.6	1.32	1.0	1.51	1.0
4	1.21	2.0	2.10	3.0	0.97	3.2	1.20	1.0	1.24	1.0
6	1.21	3.6	2.14	3.6	0.95	4.3	1.27	3.0	1.17	2.6
8	1.45	15.1	1.80	7.4	0.74	6.2	1.41	2.0	1.29	**9.9**
10	1.84	**23.3**	1.90	**9.6**	0.91	**11.4**	1.30	2.2	1.60	5.8
12	1.78	12.0	2.24	7.4	....	10.8	....	....	1.38	5.1
14	2.28	10.4	2.18	3.4						
16	2.59	4.8	2.41	4.8						
18	2.60	2.8	2.60	2.0			Subsequent			
20	....	....	2.38	2.2	Patient had		good		Patient had	
22	....	....	2.61	1.4	infection		response to		cystitis	
24	....	....	2.76	3.2			liver extract			
26	....	....	2.86	2.6						

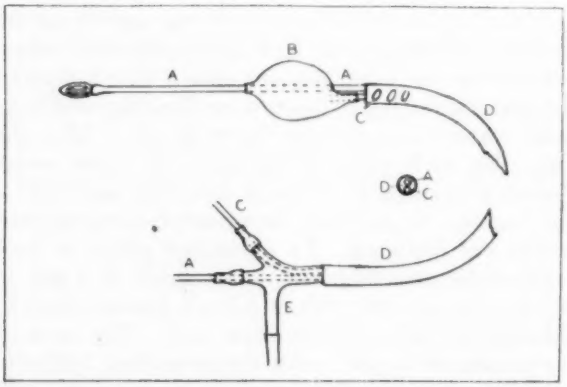
The third possibility was that the effects seen were in reality due to gastric juice necessarily present in the duodenal contents as collected by the simple technique described. This had been regarded as excluded by the fact that since the materials were incubated at a more alkaline reaction than is compatible with the proteolytic action of pepsin, the influence of this or other enzymes capable of acting only in an acid medium could be avoided. If, however, the essential reaction was not due to such enzymes, and thus could take place in a neutral environment, a technique for collecting duodenal contents, which obviously permitted gastric secretion to

enter the duodenum, would be worthless in examining the effectiveness of duodenal contents alone. Indeed, considerable gastric juice was readily demonstrated in these duodenal contents, for by means of Mett's tubes it was found that these secretions when rendered acid had a pronounced proteolytic action. Moreover from the evidence of the control periods of Cases 15 and 16 heretofore described[2] it could possibly be inferred that some effective interaction between gastric juice and beef muscle could take place at an acidity at least no greater than pH 5. It was at this reaction that these substances were administered separately to these two patients, but with the production of remissions, nevertheless, which were considered as probably due to the impossibility of completely preventing contact between the gastric juice and beef muscle within the patient. In order then to test the possibility that gastric secretions included in these duodenal contents might be the basis of the observed effects, it was decided first to test the influence of gastric contents collected entirely free from duodenal contents and then incubated with beef muscle at pH 7, and, second, if this gave a positive result to collect by a special technique duodenal contents free if possible from gastric juice.

(*e*) *The Effect of the Incubation of Beef Muscle with Normal Human Gastric Juice Containing no Duodenal Contents* (*in Neutral Solution*). The first of these experimental maneuvers was carried out on Case 33 with the results shown in Table I. Gastric juice was collected from normal subjects in the usual manner except that before the injection of histamin the fasting contents were discarded and the stomach washed with water to remove all traces of bile. After the subcutaneous injection of 0.5 mg. of histamin the juice secreted was removed with a syringe at frequent intervals and only colorless gastric juice saved. In this way the presence of regurgitated duodenal contents was obviated. Two hundred grams of beef muscle were incubated for two hours in the presence of 5 gm. of pepsin and 80 cc. of water at a pH of from 2.5 to 3.5 maintained by appropriate additions of strong hydrochloric acid. The resulting liquid was then neutralized to pH 7 with strong sodium hydroxid and to it were added from 150 to 200 cc. of the gastric juice collected as described above, which had itself been neutralized with sodium hydroxid. The mixture was next incubated for two hours and then given daily at pH 7 to the fasting patient. Since the patient had achylia gastrica it was, of course, impossible for the material at any time to become significantly acid, and any effects seen must have been due to the action of the gastric juice on the beef muscle either within the incubator or the patient's gastrointestinal tract. This procedure resulted in a prompt hematopoietic effect signalized by a maximum production of 17.1 per cent of reticulocytes on the eighth day of the therapy and an increase of total red blood cells from an initial level of 1.43 to 2.93 million per c.mm. within

eighteen days. This experiment clearly indicated the ability of the essential interaction between beef muscle and gastric juice to take place in a neutral environment and plainly demonstrated the inadequacy of the previous experiments with the normal duodenal contents to decide the point of whether the secretions of the duodenum itself were effective or not in terms of these reactions. The fact that the effective gastric juice here used contained no bile was excellent evidence that the effects previously seen in the numerous experiments with gastric juice were certainly not due to the occasional presence of duodenal contents in small amounts. Although it now appeared that the positive effects observed with the duodenal contents were in all probability due to the presence of an admixture of normal gastric juice, it remained to confirm this and to determine whether normal duodenal contents were not also capable of producing such an effect.

(*f*) *The Effect of the Incubation of Beef Muscle With Normal Human Duodenal Contents Containing no Gastric Juice (in Neutral Solution)*. Accordingly, an apparatus for collecting duodenal contents relatively free from gastric juice was constructed and is described because of its possible use to other investigators. (See illustration.)



Apparatus for collecting separately simultaneous samples of gastric and duodenal contents. *A*, Rehfuss tube to be placed with tip in duodenum for collection of duodenal contents; *B*, rubber balloon to be distended with 12 per cent sodium iodid solution and placed just proximal to the pylorus; *C*, Rehfuss tube communicating with interior of balloon; *D*, large tube containing tubes *A* and *C* and remaining in the stomach for collection of gastric juice; *E*, glass cannula for separating lumina of tubes *A*, *C* and *D*.

A rubber tube, *D*, of moderate stiffness 72 cm. long, 8 mm. in external and 6 mm. in internal diameter, was passed over two Rehfuss tubes, size No. 12 French. One tube, *A*, ending in the usual olive tip, was allowed to protrude 18 cm. beyond the lower end of the large tube *D*, after passing independently through a small pear-shaped rubber balloon *B*, some 5 cm. in length, which when just inflated had a diameter of 3 cm. and could safely

be distended to twice that size. The pear-shaped balloon was attached by its stem end, as it were, close to the end of the large tube, to the second small Rehfuss tube *C*, which thus opened into the interior of the balloon traversed by the first Rehfuss tube *A*. The points of penetration of the balloon by by the first Rehfuss tube, carrying on its end the olive, and the point of attachment of the second Rehfuss tube to the balloon were made secure against leakage by the insertion within each tube of an appropriate length of small, carefully fire-polished capillary glass tube 1 cm. in length upon which waxed thread could be appropriately wound to secure the tightness of the joints. The lower end of the large tube, *D*, was perforated for a distance of a few centimeters by a series of holes in order to give it greater flexibility and to provide a means of entrance for liquids, which could thence pass throughout the large tube *D* in the space not occupied by the two contained small Rehfuss tubes *A* and *C*. To the upper end of the large tube was fixed a glass cannula, *E*, having three branches through two of which penetrated respectively the small Rehfuss tubes, *A* and *C*, made watertight thereto by short rubber tube collars. To the third branch was fitted a short length of flexible rubber tube.

It can be seen from the diagram of this apparatus (see illus.) that three independent tubes could in this way be passed into the stomach of an accommodating subject. The first Rehfuss tube, equipped with the olive, could be observed to pass into the duodenum under the fluoroscope. The deflated balloon could now be allowed to progress to the antrum of the stomach adjacent to the pylorus, and there be dilated to a desirable degree with a 12 per cent aqueous solution of sodium iodid. The large tube, *D*, resting in the stomach could be used to remove gastric secretions and thus help the balloon to eliminate them from the duodenum, from which simultaneously the duodenal secretion was being collected following the introduction of 10 cc. of cream through tube *A*. With a little practice on the part of the subjects and the investigator it was found possible to collect about 75 cc. of duodenal juice in an hour, while often over 150 cc. of gastric juice were simultaneously removed. It thus became evident that without these special precautions a considerable quantity of gastric juice would have entered the duodenum. It was therefore not surprising to find that, in contrast to the duodenal contents previously used, the duodenal juice collected in this particular fashion, showed almost no peptic activity on being made acid. The total daily secretion of this specially collected duodenal juice by one subject, amounting to about 75 cc., was used each day in the experiment now to be described.

Two hundred grams of beef muscle were incubated for 2 hours with 50 cc. of water, 5 gm. of pepsin and sufficient strong hydrochloric acid to give a pH of from 2.5 to 3.5. The resulting liquid was then neutralized to pH 7 with sodium hydroxid and to this was added 75 cc. of the "special" duodenal juice presumably free of gastric contents, which had also previously been brought to pH 7 by the addition of a small amount of sodium hydroxid. After thorough mixing, this material was incubated for two hours and then given each day for ten days in the usual manner to the fasting patient. The result of this procedure carried out during the control period of Case 34 is shown in Table I. During this period, no evidence of clinical improvement resulted, there was some diarrhea, which was controlled by paregoric, and on the eighth day there was a trifling increase of reticulocytes to 4.8 per cent. In the succeeding test

period the procedure was identical except that 75 cc. of gastric juice collected in the usual manner were used instead of the "special" duodenal juice. That is to say, after incubation of the beef muscle with pepsin and hydrochloric acid, the mixture was neutralized to pH 7, incubated with gastric juice also at pH 7 and given at that pH to the patient. Prompt clinical improvement took place, and on the eighth day of this therapy the reticulocytes had risen to 28.4 per cent and the total red blood cells increased during a sixteen-day period from 1.21 to 2.33 million per c.mm. This result clearly indicates that in all probability the normal duodenal secretions free of gastric juice are incapable of producing an effect upon blood formation in pernicious anemia by themselves (see also Case 29, Table II) or by an action upon beef muscle; and that the effects seen in the previous observations with normal duodenal contents (Cases 28 and 32) were undoubtedly due to the presence of gastric juice. The trifling rise of reticulocytes produced by the "special" duodenal contents in the control period of this experiment is scarcely to be taken as evidence of a hematopoietic effect, but if so, is likewise due in all probability to traces of gastric juice entering the duodenum in spite of all precautions. The test period of this experiment, furthermore, amply confirms the observation made in Case 33 that the effective agent in the gastric juice can interact with the beef muscle at a neutral reaction.

The experiments so far reported make it virtually certain by the exclusion of other possible components that the intrinsic factor involved in the production of the hematopoietic substances concerned in these experiments is secreted by the normal human gastric mucosa, and so is present as a constituent of the fasting gastric juice secreted after histamin injection. Furthermore, the fact that the effective interaction of the gastric juice and beef muscle may take place in neutral solution excludes at once the possible rôle of pepsin in this process. In considering other enzymes known to be secreted by the gastric mucosa, particularly those concerned with action on protein, the properties of rennin were reviewed, this enzyme being, after pepsin, perhaps the most clearly defined. Rennin is active in neutral or very weakly acid solution,[14] and has properties of thermolability which may serve to distinguish it from pepsin.[13] Schmidt-Nielsen,[15] in experiments upon the then disputed question of the identity of rennin and pepsin, found that the neutral milk coagulating power of extracts of calf stomach could be greatly reduced by a temperature of 40 to 42° C. maintained for from one to three days in the presence of hydrochloric acid. It then appeared that such a destructive effect might have been involved in our earlier experiments with pig gastric mucosa and with pepsin. In 1928 we briefly mentioned certain negative experiments on the digestion of beef muscle with pig stomach mucous membrane, using the latter as a potential source of peptic activity after it had been

autolyzed with hydrochloric acid in the incubator.[9] We had also fed certain pernicious anemia patients 200 or more grams daily of this autolyzed pig gastric mucosa. Those experiments were either entirely negative, like those with pig pepsin[9,10] now reported in full, or showed a doubtful effect on blood formation. Recently the work of Sturgis and Isaacs[16] and of Sharp[17] now confirmed by Conner[18] and by Wilkinson,[11] has demonstrated the effectiveness of the feeding of desiccated preparations of pig stomach in pernicious anemia. An obvious difference between our experiments and those of Sturgis and Isaacs or of Conner is the successful therapeutic use by these investigators of fresh or merely dried stomach tissue. In our experiments with the pig gastric mucosa the tissue was always incubated at 37.5° C. for at least forty-eight hours in the presence of hydrochloric acid. In the preparation of commercial pepsin, a process which lasts several days, a temperature of 44.5° C. is permitted in the presence of acid.[8] Judging from the work of Schmidt-Nielsen[15] such conditions could reasonably be expected to change certain properties at least of the enzymes of the fresh gastric mucosa capable of acting at the neutral point. For these reasons it was decided to repeat our original experiments with autolyzed pig gastric mucosa incubated with beef muscle using, instead, as a potential source of enzymes, as nearly fresh pig gastric mucosa as possible.

(*g*) *The Effect of the Incubation of Beef Muscle With Pig Gastric Mucosa.* Fresh pigs' stomachs were obtained at the slaughter house, opened and washed with cold water. The mucosa was then separated from the muscular layer and placed in the icebox. Each day a suitable amount of this tissue was run through a fine meat chopper and 100 gm. of the prepared material mixed with 200 gm. of beef muscle, 4 gm. of pepsin, and enough water to give a semiliquid mass. Strong hydrochloric acid was then added until an acidity of between pH 2.5 and 3.5 was obtained and the mixture incubated for two hours. The material was then removed from the incubator, neutralized to pH 7 with sodium hydroxid, and again incubated for one hour. It was then poured through a fine strainer and given at once to the fasting patient. The data of the control period of Case 36 in Table I show the results of this procedure. An excellent remission was at once forthcoming, with a maximum production of 22 per cent reticulocytes on the eighth day at an initial red blood cell level of 1.72 million per c.mm. This positive result was comparable, according to the data of Minot and his associates,[6] to the result to be expected from the daily ingestion of about 300 gm. of liver by similar patients and was in contrast to the negative or doubtful results previously obtained under these circumstances with autolyzed mucosa or pepsin incubated with beef muscle. This same patient, Case 36, was now left without medication for a few days since the clinical condition was greatly improved; and when it was observed that the red blood cell count was again diminishing slightly the

observation of the control period was repeated in all its details, except that 25 instead of 100 gm. of the mucosa were incubated with 200 gm. of beef muscle. Again, as is shown by the data in Table I, a production of reticulocytes took place, indicating a positive effect; this time, as was to be expected as a result of the recently preceding positive therapy, the production of reticulocytes attained a maximum of only 8.6 per cent on the eighth day, with an initial count of 1.55 million red blood cells per c.mm. This treatment was discontinued on the eleventh day before an appreciable increase of red blood cells had occurred.

Sturgis and Isaacs[16] first demonstrated the effect of feeding whole, dried pig stomach in pernicious anemia. They state that the daily ingestion in this form of the equivalent of from 190 to 218 gm. of the fresh stomach tissue gave maxima of 18.8, 14.9 and 25.3 per cent of reticulocytes for corresponding initial red blood cell counts respectively of 0.95, 0.73 and 1.47 million per c.mm. These effects are roughly comparable to the result expected from the feeding of similar amounts of liver, since the first two reticulocyte percentages are below, and the last one is above the average figures of about 20, 25 and 15 per cent to be assumed from the data of Minot and his associates.[6] Since it did not seem probable that the maximal effect in the first period of the experiment just described or the distinct effect seen in the second period could have been caused by the individual action of the small amounts of pig gastric mucosa fed without supposing an interaction with the beef muscle we so stated in a recent preliminary publication.[18a] Subsequently, however, we have been forced to conclude from the results of other experiments in which definite reticulocyte responses appeared from the daily administration of as little as 30 gm. of fresh mucosa alone that the effects seen in the observations on Case 36 may have been entirely due to the independent action of the gastric mucosa. Since the incubation of this material for forty-eight hours in our original experiments or boiling for five minutes in other experiments rendered it ineffective, it is probable that the properties of this material are not those of liver extract, which is relatively heat resistant. On the other hand, the thermal conditions under which the effectiveness of the fresh mucosa is destroyed are similar to those abolishing the effectiveness of human gastric juice (Case 6[1] and Case 20) and thus suggest the probability of an action of a thermolabile factor in the mucosa upon other constituents of the gastric mucosa much as human gastric juice acts upon beef muscle. Apparently the addition of beef muscle to the fresh mucosa does not ordinarily add to the effect of the action of this factor, although, judging from the decided effects seen in the observations on Case 36, it is possible that such action may have taken place there.

As a result of the experiments so far reported, it may, then, reasonably be concluded that the intrinsic factor involved in the

production of the hematopoietic substance by interaction with beef muscle is undoubtedly secreted by the mucosa of the normal human stomach. On the contrary, it is also apparent that this intrinsic factor is not demonstrably present in normal human saliva or duodenal contents free from secretions of the gastric mucosa; nor has the patient with pernicious anemia been found able to produce the hematopoietic substance from beef muscle ingested as such, unless potentially exposed to the action of the secretions of the normal human stomach proper. Furthermore, it has been shown that this reaction between normal human gastric juice and beef muscle will take place in neutral solution. A similar reaction may apparently be carried out by the fresh mucosa of the pig's stomach, but not by the action of pig pepsin upon beef muscle or by pig stomach mucosa after prolonged incubation with acid.

Analysis of the Nature of the Extrinsic Factor. Since protein-splitting enzymes are considered to be outstanding constituents of gastric juice, it appeared entirely possible that the extrinsic factor of the effective reaction might be protein in nature. The beef muscle acted upon by the gastric juice was composed mainly of protein (22 per cent) and contained only 3 per cent of fat and perhaps 0.3 per cent of carbohydrate; and the effective principle of Cohn, Minot and their associates[19] and of West[20] was believed to be a nitrogenous base and hence possibly a derivative of protein. Perhaps, therefore, with an unjustified expectation of success it was decided to try the effect of the action of gastric juice upon the proteins of the beef muscle free from carbohydrate and fat.

(*a*) *The Effect of the Incubation of Beef Muscle Proteins With Normal Human Gastric Juice.* The preparation of sufficient quantities of protein from beef muscle in as unchanged a state as possible involved some difficulties and resulted in the failure referred to[2] in the control period of the experiment on Case 24. This failure is believed to have been due to the denaturization of the protein by the incautious addition of strong sodium hydroxid in the original solution of the proteins. A method based upon the precipitation of the muscle proteins, having an isoelectric point in the vicinity of pH 6 was eventually evolved and utilized in the experiments now reported. Two hundred grams of beef muscle were thoroughly mixed with a liter of physiologic salt solution by means of an electric stirrer, and sufficient sodium hydroxid was added to produce a pH of 9.2. The resulting solution was then allowed to stand and the fat skimmed from the surface as completely as possible. The solution was filtered through a fine wire strainer which removed the undissolved connective tissue and then diluted with more physiologic salt solution to a volume of 10 liters in a precipitating jar. After standing a few minutes the small amount of fat remaining on the surface was removed and hydrochloric acid added slowly while the mixture was stirred until a pH of 6 was reached. As this reaction

was approached a copious white precipitate appeared. After sedimentation had taken place, the hemoglobin tinged, supernatant fluid was removed and the precipitate washed twice with 10 liters of salt solution at pH 6. The protein precipitate was now placed upon compress cloth and most of the salt solution expressed. Tests of this material showed no carbohydrate and only traces of fat on ether extraction. The main constituent of the grayish-white precipitate was regarded as in all probability muscle globulin, on account of its characteristic isoelectric point.[21] All of the protein thus prepared from 200 gm. of beef muscle was used daily in the preparation of the material fed to each patient.

Since it had been shown that both gastric juice and beef muscle were individually ineffective, no control periods were required in these experiments. To each of 4 patients, Cases 25, 26, 27 and 35, were given daily after neutralization to pH 5, the material obtained after the incubation of this protein with 150 cc. of gastric juice for two hours at pH 2.5 to 3.5 in the presence of hydrochloric acid. From the data given for the test periods of these cases in Table II, it may be seen that satisfactory remissions occurred in all of these patients, the average maximum reticulocyte production being very little less than that obtained with the whole beef muscle in otherwise similar experiments. Case 27 was given each day for ten days immediately preceding the test period with beef muscle proteins, a similar period with 100 gm. of wheat gluten flour (44.8 per cent protein) after digestion with 150 cc. of gastric juice daily. No effective substance was formed by this procedure. This patient developed an infection after ten days of the successful test period with beef muscle protein which rendered it undesirable to continue the observation, and liver extract was accordingly begun before a perceptible increase of the total red blood cell count had occurred. Case 35 was also complicated by cystitis and showed subsequently to the twelve days of the test period only a slow increase of red blood cells with liver extract. In Cases 25 and 26 satisfactory total red blood cell increases were obtained with the continuation of the digested beef muscle protein.

In the observations upon a fifth patient, Case 29, a further attempt at purification of the protein was made in order to eliminate, if possible, the last traces of fat. Instead of simply twice washing the precipitate originally formed in the salt solution at pH 6, it was twice redissolved in fresh salt solution at pH 9.2 and reprecipitated at pH 6. In spite of this, traces of ether soluble materials persisted, and the material proved totally ineffective in two ten-day periods of incubation respectively with 150 cc. of normal human duodenal contents and with 150 cc. of gastric juice daily. Since this patient then showed an excellent response to liver extract, it is necessary to suppose this failure of the purified protein to react like the previous preparations as due to a difference in the

method of preparation. It is, of course, possible that some carbohydrate or lipoid substance was the basis of the previous positive results, but this seems unlikely since carbohydrate was absent and only traces of ether-soluble material were present in all the protein preparations. More probable is the explanation that the redissolving of the protein at pH 9.2 caused denaturization, or that loss of some essential protein occurred, since some precipitation was observed to occur on either side of pH 6, a value which was empirically selected as the point of approximately maximum precipitation. At any rate, on the basis of the other four positive results it appears reasonable to accept provisionally the idea that in all probability protein or some closely related substance is the extrinsic factor in the reaction between the normal human gastric juice and the beef muscle.

Discussion. The experiments described in the preceding papers of this series[1,2] made it seem highly probable that the basis of the formation of the substance effective in pernicious anemia, in terms of the hematopoietic reactions described, is the interaction of an intrinsic factor in the normal gastric juice and an extrinsic factor in the beef muscle. The observations recorded here confirm in general those already reported and delineate somewhat the nature of both factors. It can now be said with certainty that the intrinsic factor is a substance secreted by the normal gastric mucosa, since it has been demonstrated that neither normal saliva nor duodenal contents free from gastric juice are able to produce from beef muscle the effective substance, and since gastric juice free from duodenal contents is fully effective. Additional confirmation is added by the demonstration of the capacity of fresh pig gastric mucosa to produce an effective principle of similar hemolability. These observations, furthermore, correlate perfectly, on the one hand, a clearly demonstrated ability of the secretions of the normal gastric mucosa to produce by interaction with beef muscle a substance capable of promptly relieving patients with pernicious anemia of their anemia and, on the other hand, the total inability of these patients, whose outstanding and irremediable defect is a persistent achylia gastrica, to produce in themselves such a substance from beef muscle. The experiments are, then, uniformly in support of our original conception of the nature of the disease Addisonian pernicious anemia as due to a virtual deficiency brought about, even in the presence of a diet adequate for the normal individual, by defective gastric digestion of protein as a result of the achylia gastrica.

The most obvious objection that can be raised to this unqualified position is that many individuals, without clear evidence of pernicious anemia, appear to have a marked inability to secrete hydrochloric acid in the stomach. This is indeed a difficult problem even though the number of such individuals can be materially reduced

by the discrimination possible by modern methods of gastric analysis. By the use of the fractional alcohol meal[22] followed by histamin injection[3] many of the so-called cases of achlorhydria in individuals without pernicious anemia can be eliminated, but there remain not a few with an achlorhydria which the best methods will not serve to differentiate from the gastric condition found in manifest cases of pernicious anemia. Frequently, however, a critical study of the blood of such individuals shows evidence of abnormal marrow activity even with red blood cell counts and hemoglobin concentrations within normal limits. Some of these individuals have a definite anemia of a secondary or chlorotic type, particularly the members of the families of patients with pernicious anemia[23,24] and a few such cases have been observed later to develop pernicious anemia.[25] It is therefore possible that even with an apparently complete loss of acid secretory power, considerable time is necessary for the elimination of a hypothetic supply of preventive principle from the body. It is even conceivable that small amounts of the effective substance are normally ingested with animal foods other than liver or kidneys,[26] particularly since there is now evidence of a possible gradual failure of the absorptive capacity of the intestinal tract for the necessary substance, suggested by the differences in the amounts of liver extract necessary to maintain a normal red blood cell count in different pernicious anemia patients.[27]

However, to give an answer to the problem, it is only necessary to point out that the present experiments demonstrate that the effective principle can be made by the interaction of normal gastric juice and beef muscle in a neutral environment (Cases 33 and 34), and that the activity in this respect of normal human gastric juice cannot be simulated by the action of pepsin and hydrochloric acid on beef muscle (Cases 9, 10 and 21). With this elimination at one stroke of the relevance of the time-honored essentials of gastric analysis, the hydrochloric acid and the pepsin determinations, no necessarily applicable test remains at the moment for the detection of what kind of gastric juice may contain the essential factor. It is now plainly an unwarranted assumption to suppose that the titration of acidity and the estimation of pepsin are necessarily of value for detecting the essential constituent of effective gastric juice. Although it is probable that the absence of both hydrochloric acid and pepsin from the gastric contents may often indicate also the absence of this other essential, such is certainly not necessarily the case.*

On the other hand, the explanation of the disease on the basis of

* We now have unpublished data showing that the gastric juice of two cases of chronic chlorosis and one of idiopathic achlorhydria with a normal blood, all of which were totally unable to secrete hydrochloric acid, was as effective, after incubation with beef muscle, as normal human gastric juice under those circumstances in bringing about remission in cases of pernicious anemia.

an achylia gastrica may be objected to because occasionally cases with the blood picture of pernicious anemia are reported with an apparently normal gastric function.[28,29] It is not contended that the mechanism now disclosed by these experiments as the probable basis of cases of pernicious anemia with achylia gastrica is the sole mechanism for producing all instances of the disease. However, it is perhaps highly significant that the commonly alleged causes of pernicious anemia are all potentially related to the function of the gastrointestinal tract. With many of these, indeed, there is a coëxisting achylia, but there may be an apparently normal gastric function, in terms, it is true, of tests which are here shown to be not necessarily discriminative. The belief that abnormality of the gastrointestinal tract in pernicious anemia has a causal relationship to the disease is not new and is, in our opinion, well founded on numerous clinical and certain experimental facts. The clinical evidence that achylia gastrica as produced by hereditary influences, chronic alcoholism, extensive cancer and gastric resection is responsible for certain cases, has already been reviewed[1,30] and the probable mechanism clearly demonstrated.[2] Cases of anemia closely simulating the blood picture of pernicious anemia with apparently normal gastric secretions have been reported[28,29] and encountered in our experience,* but in such instances there have usually been other disturbances of the intestinal tract such as short circuits of the small intestines[31] or chronic diarrhea.[32] Partial obstructions[33,34] or diseases associated with persistent gastrointestinal tract symptoms such as sprue,[35,36] pellagra[37] or infestation with tapeworm[38] or other intestinal parasites[39] have been given as causes of pernicious anemia. In most of these cases, however, there was stated to be an absence of free hydrochloric acid from the gastric contents. Seyderhelm[40] has reported experiments of great interest in which, by producing a stenosis of the small intestine in dogs, in 2 out of 10 animals a blood picture resembling pernicious anemia has been produced.

When interpretations of these different observations have been attempted it has usually been in terms of the action of hypothetic toxins. It now appears possible to explain these apparently divergent causes of a single disease entity on a uniform basis by the logical consequences of the mechanism revealed by our experiments. Since the effective substance has been shown to be formed within the lumen of the normal human stomach, unless it is to be lost to the uses of the organism, it must be absorbed from some part of the gastrointestinal tract. Furthermore, it can now be stated that although the effective mixture of gastric juice and beef muscle

* The gastric juice of two such cases has recently been tested for its ability to produce the effective principle from beef muscle, and although containing normal amounts of hydrochloric acid, pepsin and rennin, was found to be totally ineffective.[18a]

appears to have an effect on blood formation identical with that of the material contained in liver when either is given by mouth[6,7] or when the latter is given by rectum[41] or intravenously,[42] it has an entirely different thermostability from the principle contained in liver. Now, if it be assumed that the final effective substance, in terms of the hematopoietic reactions, is a single substance, and that substance the one contained in liver, it follows that at some point between the stomach and the bone marrow a conversion of the effective principle created by the presence of beef muscle in the normal stomach into the active principle present in liver must occur. This suggestion is enough to indicate the possibility that any one of a series of defects relating either to the chemistry of the hypothetic conversion process, or certainly to the absorption or distribution within the body of the final effective principle may result in a deficiency of the final effective substance. Next to a defect of the original formative process within the stomach, the loss of the absorptive power of the intestinal tract either mechanically or by bacterial invasion, or the destruction in the bowel of the effective principle after formation would be the most obvious ways in which a deficiency of the final effective substance could be brought about. These remarks indicate that a defect of gastric function alone is not necessarily the only way in which, quite in accord with our hypothesis of the nature of the disease, a deficiency of the necessary substance might be produced.

The experiments reported in this paper add confirmation to the idea that the intrinsic factor of the essential mechanism of the normal stomach for the production of the effective principle resides in the secretions of the normal gastric mucosa itself. That neither normal saliva (Case 23) nor duodenal contents free from gastric contents are effective agents has been clearly shown (Case 34); and that the pernicious anemia patient is totally impotent in this respect has been directly proved[1] (Cases 1, 4 and 10). The present experiments plainly demonstrate, however, that the process is not necessarily due to an enzyme action in an acid medium as was before tentatively suggested by us.[2,10] That hydrochloric acid alone is not responsible for this reaction has already been amply demonstrated.[1,2] (Cases 2, 16 and 17.) That an acid hydrolysis by pepsin is not the basis of the observed activity is evidenced by the negative effects of the incubation of beef muscle with pepsin and hydrochloric acid (Cases 9, 10, 21, etc.). Indeed, the supposition that an acid environment is necessary for the essential process is eliminated by the demonstration of the positive effect of normal gastric juice on beef muscle at the neutral point (Cases 33 and 34). That an organic substance in the normal gastric juice is acting upon the beef muscle is suggested by the demonstration that the subsequent hematopoietic reaction is lacking if the gastric juice has been heated to from 70° to 80° C. for a half hour before incubation with the beef muscle.

The problem of the nature of the intrinsic factor, therefore, narrows itself to a consideration of what thermolabile constituent of the secretions of the normal gastric mucosa acting in a neutral environment can be responsible. The preparation of relatively pure proteins from the beef muscle without noteworthy diminution of the usual effects seen in the other cases on incubation of whole beef muscle with gastric juice, suggests that the extrinsic factor of the reaction is a protein or closely related substance, not carbohydrate or fat. This observation agrees with the work of Cohn, Minot and their collaborators,[19,42] and with that of West,[20,43] who have independently obtained evidence that the active principle of liver extracts effective in the treatment of pernicious anemia is in all probability a nitrogen-containing substance, possibly a nitrogenous base. Since other functions of the gastric juice are carried out by enzymes, it is perhaps reasonable to continue to regard the essential action as possibly due to an enzyme. The destruction of the activity of the gastric juice by heating to from 70° to 80° C. for a half hour is consistent with that idea,[14] although damage to factors other than enzymes could have been brought about. The two important enzymes, capable of acting on protein, which are secreted by the gastric mucosa itself are pepsin and pararennin, or the rennin of the adult stomach.[13,14] If by pepsin is understood an enzyme acting optimally in the vicinity of pH 2 and not at less acid ranges than pH 4, this enzyme or its like can be at once excluded from consideration, since it has been shown that the essential reaction may take place in a neutral solution (Cases 33 and 34). On the other hand, adult rennin satisfies this requirement and is destroyed under the conditions abolishing the effectiveness of the human gastric juice,[14] and certainly greatly reduced under the conditions employed in the preparation of commercial pepsin from the gastric mucosa of the pig,[8,15] shown above to have been incapable of the essential interaction with beef muscle. Since other proteolytic enzymes have also been found in human gastric juice, and since it is possible that the effective substance is not an enzyme, it is impossible to define more exactly at present the nature of this essential and heretofore unrecognized function of the normal human stomach.

The original demonstration[1,9] that the patient with pernicious anemia even under the most favorable conditions cannot form a hematopoietic substance in detectable amounts from beef muscle has now received ample confirmation. The observations of the control periods of Cases 1, 4 and 10, reported in the first paper; of Cases 13, 15 and 17, reported in the second paper; and of Cases 9,*

* The data on Case 9 are given in the table of the first paper of this series[1] as having no control period because the negative control period with pepsin and hydrochloric acid considerably preceded the effective test period with stomach contents. For convenience in Table I of the present paper the test period is given as immediately following.

10,* 20, 21, 23 and 34 now reported, comprising in all 12 periods of observation, show no significant effects of 200 or more grams of beef muscle either fed as such, or after incubation with hydrochloric acid, with pepsin and hydrochloric acid, with normal saliva or with normal duodenal contents containing no gastric juice. This group of experiments clearly indicates that there is no effective substance present in detectable amounts in beef muscle, and that the patient with pernicious anemia cannot carry out the effective reaction easily demonstrable with the secretions of the normal gastric mucosa. The data already presented indicate that it is improbable that the essential defect in pernicious anemia resides in a dysfunction of the salivary or duodenal secretions, but in the patently defective gastric juice. This agrees with the observations of others[12] and ourselves that the enzyme activity of the duodenal contents of patients with pernicious anemia are essentially normal. The well-known defect of the secretions of the gastric mucosa itself in these patients is thus further brought into prominence and the contrast with the unique and repeatedly demonstrated effectiveness of the secretions of the normal gastric mucosa is emphasized. These facts, we believe, constitute important further confirmation of the original working hypothesis of the nature of the disease set forth in the first paper of this series.[1]

It may then be stated as a result of the experiments reported in this series of papers that:

A marked hematopoietic effect associated with general clinical improvement may be observed with regularity in patients with uncomplicated Addisonian pernicious anemia by permitting the absorption from the gastrointestinal tract of such patients of some substance, or substances, generated in vivo *or* in vitro *by an interaction of an intrinsic factor (a) and an extrinsic factor (b). An intrinsic factor (a) secreted by the active normal gastric mucosa, and not present in detectable amounts in the gastrointestinal tract of patients with pernicious anemia or in normal saliva or duodenal contents free of gastric juice. The factor may be characterized as probably organic in nature, destroyed by exposure to a temperature of between 70° and 80° C. for a half hour, or to 44.5° C. for several hours; possibly an enzyme; and active in neutral solution. An extrinsic factor (b) probably protein, or of a closely related nature, obtained by isoelectric precipitation from beef muscle at pH 6.*

The evidence from the quantitative action of liver, kidney, and in particular small amounts of potent liver extracts, as has already been pointed out, is clearly in favor of pernicious anemia as a type

* Similarly, the data of Case 10 are given in the table of the first paper of this series[1] as consisting of a negative control period of beef muscle feeding immediately followed by a positive test period with stomach contents. In Table I of the present paper a different negative control period with pepsin and hydrochloric acid is shown, which actually was continuous between the control and test periods of the experiments shown in the table of the first papers of this series.

of deficiency disease.[1,9,10,44,45] Two or more of its three salient features, gastrointestinal disturbances, neurologic disorders and anemia are found in other diseases now known to be due in part, at least, to a deficiency of the diet, such as pellagra, sprue and beriberi. Our more recent experiments make it appropriate to consider more fully our conception of the disease as due to a virtual deficiency produced not by a defective diet in the usual sense, but by a defect in the patient. It is to be remembered that until food is absorbed from the gastrointestinal tract it is still outside of the body in a functional sense. We believe that our conception of the disease as a deficiency of a new type, brought about indirectly by a defect of the individual which conditions a deficiency not existing for the normal individual, explains the lack of convincing evidence for a direct dietary deficiency. This does not preclude the possibility that abnormal diets may hasten the development of the anemia or have a relationship to the original gastric dysfunction. This conception of the deficiency mechanism has the advantage of simplicity, and now possibly the merit of objective support from our experiments and their recent confirmation by others.[11,46] It has not been possible to secure palpable results with any of the known vitamins, iron, copper, or even extracts of the liver itself other than certain preparations containing with further purification increasing amounts of nitrogen possibly in the form of a nitrogenous base.[19,20] Indeed, the conception of the disease as due to a direct deficiency of the food in respect to any of the known vitamins is untenable from numerous observations upon the nature of the effective principle of liver extract already reported by Cohn, Minot and their associates,[19] and particularly in the face of the experiments reported in the second paper of this series.[2] Therein it was shown (Cases 13, 15 and 17) that certain amounts of beef muscle and normal human gastric juice, if given without opportunity for contact, were ineffective in producing the remissions at once forthcoming if the same amounts of the identical substances were given a chance for interaction. It is difficult to see even a reasonable analogy to the occasional spontaneous recovery of certain animals fed diets deficient in vitamin B, since it is probable that this phenomenon, known as "refection," is due to the fact that bacterial action within the gastrointestinal tract is able to synthesize under certain special conditions the vitamin lacking in the diet.[47] If the remission in these patients is the response to a "vitamin," it must then be assumed that its synthesis has taken place by an interaction between beef muscle protein and normal human gastric juice.

The facts demonstrated by our experiments present, in our opinion, without invoking the aid of other hypothetic factors, a working concept of the mechanism of pernicious anemia. The peculiar nature of the bone-marrow pathology in relapse[48] and its highly specific response to particular extracts of liver or to the

products of specific reactions between beef muscle proteins and normal human gastric juice are far more comprehensible as a response to the supplying of a particular deficient substance than as due to the neutralization of "toxins" of so far undemonstrated existence. As Whipple[49] has pointed out, the arguments for the presence of a toxin are quite as good when used as evidence for a deficiency. The possibility of microörganisms within the gastro-intestinal tract acting as a source of toxins[50] capable of damaging the bone-marrow or destroying the blood corpuscles[51] has been practically eliminated in the opinion of Davidson[52] by more critical studies of the bacteriology before and after liver therapy. To the clinician familiar at first hand with the quantitative nature of the response of pernicious anemia patients to the administration of a few grams of material constituting adequate liver extract therapy there is something wholly unsatisfactory in conceptions of the etiology of the disease involving toxins.

It is therefore not surprising that since the original demonstration of the effectiveness of liver therapy in pernicious anemia by Minot and Murphy[53] has been so amply confirmed, the idea has arisen that a defect of the human liver,[54,55] or of some organ of the human body analogous to those of the normal animal known to be effective when fed by mouth, might be directly responsible for the development of the disease. Unfortunately, this attractively simple conception does not correlate well with constant, recognizable pathology in the patient except in the case of the dysfunction of the stomach. Also, it is not easy to see why the liver, the kidney[53,56] and possibly other organs should apparently compete as primary sites of formation of the effective substance unless possibly they are merely storage depots for material formed elsewhere in the normal animal. More logical interest attaches to the recent observations of Sturgis and Isaacs,[16] Sharp,[17] Conner[18] and Wilkinson,[11] who have reported marked hematopoietic effects with pig stomach feeding or with extracts of that organ. Sturgis and Isaacs suggest that their experiments give evidence in support of our own, but state that they are at present uncertain whether the effective principle involved is merely present in the stomach of these animals as it is in the liver or kidney or whether it is formed therein by normal physiologic processes or postmortem autolysis. The last possibility was the one originally investigated by us in 1928 with negative results, using pig-stomach mucosa after incubation at 37.5° C. for forty-eight hours in hydrochloric acid.[9] We have now been able by the administration of 25 or 100 gm. of fresh pig gastric mucosa with or without beef muscle to reproduce the activity of human gastric juice and beef muscle. Since, in contrast to the relative thermostability of liver or liver extract, we have found that boiling for five minutes or incubation in acid for forty-eight hours will destroy completely the effectiveness of pigs' gastric mucosa or of human gastric juice,

we consider that the mechanism of the action of the whole stomach tissue, demonstrated by Sturgis and his associates, is in all probability identical with that involved in our earlier experiments with human gastric juice and beef muscle.

It is perhaps unnecessary to point out, furthermore, that the effectiveness of the whole pig stomach or mucosa after the death of the animal does not necessarily imply the existence of a physiologic process within the gastric tissue itself resulting in the production of similar effects during life, since it involves an artificial set of conditions which do not exist in the case of the physiologic action of normal human gastric juice upon ingested beef muscle in the lumen of the stomach.[1] This distinction between an action of the stomach alone and an action upon its contents is inherent in the hypothesis of the disease which we have advanced, and was expounded in presenting the great significance, for the interpretation of our experiments, of the question of whether the gastric juice of the normal individual was itself effective or only after an interaction with beef muscle.[2] The classical riddle of gastric physiology as to why the stomach does not digest itself (to form "liver extract") might again become perplexing were it necessary to assume that the mechanism for the formation of the substance responsible for the effects seen in the studies with pig stomach was not merely a simulation postmortem of the physiologic action of the secretions of the normal stomach on its contents during life.

As always, however, in science, the "explanation" explains nothing in a final sense; but it may serve to indicate a profitable direction for further searching. For this reason we have pointed out before[10] a possible analogy between diabetes mellitus and pernicious anemia. Fortunately, through the pioneer work of Banting and Best and of Minot and Murphy, an effective means of control of both diseases has been discovered. The analogy rests also upon the fact, that if our observations and conclusion are confirmed by others, a defective function of one organ of the body will have again been shown to be the basis of a remote or general disturbance. In the case of diabetes the faulty organ is known to be the pancreas; in Addisonian pernicious anemia it is probably the stomach. In diabetes, the internal metabolism of the carbohydrate and fat are disturbed; in pernicious anemia we have tried to show that some step is missing in the manipulation of proteins, external to the body in the biologic sense, although within the gastrointestinal tract. We point out as a final aspect of this analogy, in the hope that it may serve as a directive stimulus to further work, that except for a few special and obvious causes, the nature of the pathologic processes leading to the all-important dysfunction of the islands of Langerhans in the one disease and of the gastric mucosa in the other are as yet unknown.

Summary and Conclusions. 1. The validity of the hypothesis that the genesis of the disease pernicious anemia is dependent upon an inadequate gastric digestion of protein, thus permitting the development of a virtual deficiency in the presence of a diet adequate for the normal individual has been further examined and the nature of the postulated gastric defect somewhat defined.

2. The results of the following observations on cases of Addisonian pernicious anemia are considered to confirm and further characterize those reported in the previous two papers of this series[1,2] therein stated to be consistent with the above hypothesis.

(*a*) To one patient was given daily for eight days, without effect on blood formation, the material resulting from the incubation of 200 gm. of beef muscle with normal human saliva.

(*b*) To another patient was given daily for ten days, without significant effect on blood formation, the material resulting from the incubation of 200 gm. of beef muscle at pH 7 with 75 cc. of normal human duodenal contents, obtained in such a manner as to contain a minimum of gastric secretion. In each of two other patients similarly treated with beef muscle incubated with normal duodenal contents at pH 7 known to contain gastric secretion, a distinct effect on blood formation was obtained similar to that previously observed with beef muscle and normal gastric contents.

(*c*) To each of three patients was given daily for a period of at least ten days, without effect on blood formation, the material resulting from the incubation of 200 gm. of beef muscle with from 2 to 5 gm. of commercial pepsin (pig) and hydrochloric acid at pH 2.5 to 3.5, for from two to twenty-four hours before neutralization and administration to these patients at pH 5.

(*d*) To another patient was given daily for ten days, without effect on blood formation, the material resulting from the incubation of 200 gm. of beef muscle with 150 cc. of fasting normal human gastric contents (secreted after histamin stimulation) which had been previously heated to a temperature of from 70° C. to 80° C. for a half hour.

(*e*) To each of four patients was given daily during test periods of at least ten days the material resulting from the incubation of 200 gm. of beef muscle for two hours with from 75 to 150 cc. of fasting normal human gastric contents secreted after histamin stimulation. In 2 patients the incubation was conducted as usual in the presence of hydrochloric acid at pH 2.5 to 3.5 with subsequent administration to the patient at pH 5; in the other 2 patients both incubation and administration were carried out at pH 7. In the experiments performed with incubation at pH 7 the normal fasting gastric contents used were collected in such a way as to contain no duodenal contents. In all of these patients a marked and progressive effect on blood formation was observed to take place within ten days.

(*f*) In two periods of observation on one patient 100 and 25 gm. respectively of fresh pig stomach mucous membrane were incubated with 200 gm. of beef muscle, and the resulting material administered daily for two periods of at least ten days each, in both instances with a marked effect on blood formation. Subsequent experiments have indicated the probable independent action of the pig gastric mucosa in these observations.

(*g*) To each of 5 patients was given daily for at least ten days the material resulting from the incubation of 150 cc. of normal human fasting gastric contents with the washed proteins precipitable at pH 6 from 200 gm. of beef muscle previously dissolved in salt solution at pH 9.2. In all but one of these patients a marked effect upon blood formation appeared within ten days as indicated by characteristic increases of reticulocytes progressing to maxima not significantly less than those obtained in similar experiments with whole beef muscle incubated with gastric contents. In one patient no effect on blood formation occurred.

3. From a consideration of the above experiments and of those of the two preceding papers of this series, the following conclusions were drawn:

(*a*) The active constituent (Intrinsic factor) of the normal human fasting gastric contents is in all probability secreted by the mucosa of the stomach and is not detectably present in normal saliva or duodenal contents free of gastric juice, or in the secretions of any portion of the gastrointestinal tract of the pernicious anemia patient.

(*b*) This substance is probably organic, thermolabile, possibly an enzyme, capable of interaction with protein (Extrinsic factor) or closely related substances in neutral solution, resulting in the production of material having, when administered to pernicious anemia patients, a marked hematopoietic effect. If an enzyme, it is certainly not pepsin; its properties as so far determined are only in certain respects similar to those of rennin.

(*c*) The lack of this particular property (Intrinsic factor) of the gastric contents in pernicious anemia is probably the essential defect leading to the development of the disease, through a failure of the normal reaction, occurring in these experiments with beef muscle proteins, (Extrinsic factor) and normal human gastric juice.

4. It is also concluded that the existing tests for hydrochloric acid and pepsin of the gastric juice are not necessarily of value in determining the presence or absence of the intrinsic factor essential to the reactions between normal human gastric juice and beef muscle described in these papers.

NOTE.—We gratefully acknowledge the kind coöperation of Dr. James H. Means and Dr. Wyman Richardson of the Massachusetts General Hospital. The technical studies on the blood were largely performed by Miss Margaret Evans and Miss Anne Ryan.

BIBLIOGRAPHY.

1. Castle, W. B.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia. I. The Effect of the Administration to Patients with Pernicious Anemia of the Contents of the Normal Human Stomach Recovered After the Ingestion of Beef Muscle, Am. J. Med. Sci., 1929, **178**, 748.

2. Castle, W. B., and Townsend, W. C.: Ibid. II. The Effect of the Administration to Patients with Pernicious Anemia of Beef Muscle After Incubation With Normal Human Gastric Juice, Am. J. Med. Sci., 1929, **178**, 764.

3. Gompertz, L. M., and Vorhaus, M. G.: Studies on the Action of Histamin on Human Gastric Secretion, J. Lab. and Clin. Med., 1925, **11**, 14.

4. Levine, S. A., and Ladd, W. S.: Pernicious Anemia: A Clinical Study of One Hundred and Fifty Consecutive Cases with Special Reference to Gastric Anacidity, Bull. Johns Hopkins Hosp., 1921, **32**, 254.

5. Teschendorf, H. J.: Zur Differenzierung der Achylien durch fraktionierte Magenausheberung nach Histamininjektion unter gleichzeitiger Untersuchung des Harnpepsins, Deutsch. Arch. f. klin. Med., 1927, **155**, 43.

6. Minot, G. R., Murphy, W. P., and Stetson, R. P.: The Response of the Reticulocytes to Liver Therapy: Particularly in Pernicious Anemia, Am. J. Med. Sci., 1928, **175**, 581.

7. Minot, G. R., Cohn, E. J., Murphy, W. P., and Lawson, H. A.: Treatment of Pernicious Anemia with Liver Extract: Effects Upon the Production of Immature and Mature Red Blood Cells, Ibid., 1928, **175**, 599.

8. Wood, H. C., and LaWall, C. H.: The Dispensatory of the United States of America, 21st ed., Philadelphia, J. B. Lippincott Company, 1921, p. 821.

9. Castle, W. B., and Locke, E. A.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia, J. Clin. Inves., 1928, **6**, 2.

10. Castle, W. B.: The Ætiological Relationship of Achylia Gastrica to Pernicious Anemia, Proc. Roy. Soc. Med., 1929, **22**, 58; Ibid., Achlorhydria and Pernicious Anemia, British Med. J., 1929, i, 1120.

11. Wilkinson, J. F.: Pernicious Anemia, British Med. J., 1930, i, 236.

12. McClure, C. W., Montague, O. C., and Mortimer, E.: Pancreatic Function in the Absence of Hydrochloric Acid from the Stomach, Boston Med. and Surg. J., 1924, **190**, 357.

13. Mathews, A. P.: Physiological Chemistry, 3d ed., New York, William Wood & Co., 1921.

14. Waksman, S. A., and Davison, W. C.: Enzymes, Baltimore, Williams & Wilkins Company, 1926.

15. Schmidt-Nielsen, S.: Uber die vermeintliche Identität von Pepsin und Chymosin, Ztschr. f. physiol. Chem., 1906, **48**, 92.

16. Sturgis, C. C., and Isaacs, R.: Desiccated Stomach in the Treatment of Pernicious Anemia, J. Am. Med. Assn., 1929, **93**, 747.

17. Sharp, E. C.: An Antianemic Factor in Desiccated Stomach, J. Am. Med. Assn., 1929, **93**, 749.

18. Conner, H. M.: The Treatment of Pernicious Anemia with Swine Stomach, J. Am. Med. Assn., 1930, **94**, 388.

18a. Castle, W. B., Townsend, W. C., and Heath, C. W.: Further Observations on the Etiological Relationship of Achylia Gastrica to Pernicious Anemia. Proc. Meet. Am. Soc. Clin. Invest., May 5, 1930, in press. J. Clin. Invest. Lancet, 1930, **218**, 1062.

19. Cohn, E. J., Minot, G. R., Alles, G. A., and Salter, W. T.: The Nature of the Material in Liver Effective in Pernicious Anemia, II., J. Biol. Chem., 1928, **77**, 325.

20. West, R., and Nichols, E. G.: Liver Fractions in Pernicious Anemia, J. Clin. Inves., 1928, **6**, 3.

21. Salter, W. T.: Certain Physico-chemical Characteristics of Muscle Globulin, Proc. Soc. Exp. Biol. and Med., 1926, **24**, 116.

22. Keefer, C. S., and Bloomfield, A. L.: The Significance of Gastric Anacidity, Bull. Johns Hopkins Hosp., 1926, **39**, 304.

23. Faber, K., and Gram, H. C.: The Association of Achylia and Anemia of Different Types in Three Members of the Same Family, and the Behavior of the Color Index in Pernicious Anemia, Arch. Int. Med., 1924, **34**, 827.

24. Faber, K., and Gram, H. C.: Relations Between Gastric Achylia and Simple and Pernicious Anemia, Arch. Int. Med., 1924, **34**, 658.

25. Gram, H. C.: Undersøgelser over den perniciøse anaemis udvikling paa en familie med. talrige tilfaede (Meddelelse fra praxis), Ugeskrift for Laeger, 1929, **91**, 1135.

26. Elders, C.: Tropical Sprue and Pernicious Anemia, Lancet, 1925, i, 75.

27. Minot, G. R.: Some Fundamental Clinical Aspects of Deficiencies, Ann. Int. Med., 1929, **3**, 216.

28. Grinker, R. R.: Pernicious Anemie, Achylia Gastrica and Combined Cord Degeneration and Their Relationship, Arch. Int. Med., 1926, **38**, 292.

29. Munford, S. A.: Atypical Anemias, Clifton Med. Bull., 1925, **11**, 139.

30. Cornell, B. S.: The Etiology of Pernicious Anemia, Medicine, 1927, **6**, 387.

31. Little, W. D., Zerfas, L. G., and Trusler, H. M.: Chronic Obstruction of the Small Bowel, J. Am. Med. Assn., 1929, **93**, 1290.

32. Richardson, W., and Klumpp, T. G.: Sprue: Report of a Case Treated with the Authorized Liver Extract Effective in Pernicious Anemia, New England J. Med., 1928, **199**, 215.

33. Faber, K.: Perniciöse Anämie bei Dünndarmstricturen, Berl. klin. Wchnschr., 1897, **34**, 643.

34. Meulengracht, E.: Pernicious Anemia in Intestinal Stricture, Acta med. scand., 1929, **72**, 231.

35. Wood, E. J.: Pernicious Anemia in Its Relationship to Sprue, Am. J. Med. Sci., 1925, **169**, 28.

36. Baumgartner, E. A., and Smith, G. D.: Pernicious Anemia and Tropical Sprue, Arch. Int. Med., 1927, **40**, 203.

37. Mollow, W., and Klein, B.: Beiträge zur Klinik der Pellagra, Arb. ü. Tropenkrankh., 1927, p. 349.

38. Isaacs, R., Sturgis, C. C., and Smith, M.: Tapeworm Anemia, Arch. Int. Med., 1928, **42**, 313.

39. Logan, A. H.: Balantidium Coli and Pernicious Anemia: Report of Four Cases, Am. J. Med. Sci., 1921, **162**, 668.

40. Seyderhelm, R., Lehmann, W., and Wichels, P.: Experimentelle intestinale perniziöse Anämie beim Hund, Klin. Wchnschr., 1924, **3**, 1439.

41. Reznikoff, P.: Rectal Administration of Liver Extract (Cod), J. Am. Med. Assn., 1929, **93**, 367

42. Cohn, E. J., McMeekin, T. L., and Minot, G. R.: The Nature of the Material Effective in Pernicious Anemia, III, Am. J. Physiol., 1929, **90**, 316.

43. West, R., and Howe, M.: Liver Fractions in Pernicious Anemia, J. Clin. Inves., 1929, **1**, 495.

44. Means, J. H., and Richardson, W.: Impressions of Nature of Pernicious Anemia in Light of the Newer Knowledge, J. Am. Med. Assn., 1928, **91**, 923.

45. West, R.: Pernicious Anemia as a Deficiency Disease, Ann. Int. Med., 1929, **3**, 132.

46. Ungley, C. C.: The Stomach and Pernicious Anemia, Newcastle Med. J., October, 1929.

47. Fridericia, L. S., Freudenthal, P., Gudjonnsson, S., Johansen, G., and Schoubye, N.: Refection, a Transmissible Change in the Intestinal Content, Enabling Rats to Grow and Thrive Without Vitamin B in the Food, J. Hyg., 1927, **27**, 70.

48. Peabody, F. W.: The Pathology of the Bone Marrow in Pernicious Anemia, Am. J. Pathol., 1927, **3**, 179.

49. Whipple, G. H.: Hemoglobin Construction Within the Body as Influenced by Diet Factors, Am. J. Med. Sci., 1928, **175**, 721.

50. Hurst, A. F., and Bell, J. R.: The Pathogenesis of Subacute Combined Degeneration of the Spinal Cord with Special Reference to Its Connection with Addison's (Pernicious) Anemia, Achlorhydria, and Intestinal Infection, Brain, 1922, **45**, 266.

51. Seyderhelm, R.: Die Lebertherapie der perniziösen Anämie, Ergeb. d. ges. Med., 1929, **13**, 521.

52. Davidson, S.: The Ætiology of Pernicious Anemia: A Review of the Factors Concerned in Its Production, Edinburgh Med. J., 1928, **35**, 322.

53. Minot, G. R., and Murphy, W. P.: Treatment of Pernicious Anemia by a Special Diet, J. Am. Med. Assn., 1926, **87**, 470.

54. Harris, S.: Etiology of Pernicious Anemia: Is It Secondary to Hepatic Infection, Resulting in Deficiency of Liver Endocrine? Internat. Clin., 1928, **2**, 120.

55. Schwarz, E.: Megaloblastisches Blutbild und Leber, Wien. klin. Wchnschr., 1928, **41**, 192.

56. McCann, W. S.: Effect of Kidney on Blood Regeneration in Pernicious Anemia, Proc. Soc. Exp. Biol. and Med., 1928, **25**, 255.

THE NORMAL FILAMENT AND NONFILAMENT POLYMORPHONUCLEAR NEUTROPHIL COUNT: ITS PRACTICAL VALUE AS A DIAGNOSTIC AID.

By David L. Farley, M.D., Huston St. Clair, M.D.,
and
John A. Reisinger, M.D.,
Philadelphia, Pa.

(From Medical Service A, Pennsylvania Hospital, Philadelphia, Pa., and the Cooper Hospital, Camden, N. J.)

In 1904, Arneth brought forward his classification of the neutrophilic leukocytes. He separated them into five classes, according to the number of nuclear lobes of the cell. Those with a slightly indented or band-shaped nucleus were placed in Class 1, those with two lobulations in Class 2, those with three lobulations in Class 3, and so on. He determined that the occurrence of these cells in a normal individual was as follows:

Class 1	5 per cent
Class 2	35 per cent
Class 3	41 per cent
Class 4	17 per cent
Class 5	2 per cent

He thought that as a polymorphonuclear neutrophil increased in age and differentiation, the number of lobulations increased from Class 1 upward to or beyond Class 5. He believed that a cell of three nuclear lobes was an older and a more differentiated cell than one with a single lobulation. An acute infection with leukocytosis caused a "shift to the left," that is, a higher percentage of cells were found in the groups toward the left of the written page. Subsequent experimentation served to substantiate most of Arneth's conclusions in regard to his index of the polymorphonuclear cells, especially the important fact of "the shift to the left" in the presence of stimulation of the myeloid tissue by infection. The Arneth count, however, has fallen into disuse because of its complexity and the labor required in estimating the different classes.

Schilling (1920) devised a simpler index. He divided the granular neutrophilic leukocytes into four classes, viz., with simple round nucleus (myelocyte), with slightly indented nucleus (young form of metamyelocyte), with deeply indented nucleus (band form of metamyelocyte), and with segmented nucleus. He established that an average of about 4 per cent of the total leukocytes are band forms. Schilling and others have considered serial differential counts with consideration of the quantitative changes of neutrophils (nuclear shift) of far more importance than the total leukocyte count. Pons and Krumbhaar (1924) suggested that all essentials for clinical

purposes would be served if all neutrophils were divided into three classes: (1) metamyelocytes (very young)—with round or slightly indented nuclei; (2) nonsegmented forms (young)—when the nuclear material was connected by broad bands; (3) segmented forms (older)—when two or more groups of nuclear material were joined by narrow filaments. Piney (1928) would disregard in the routine count Schilling's Class 1 and 2 (myelocytes and young forms of metamyelocytes), since they appear so seldom in infection as to be of little clinical significance.

Cooke and Ponder (1927) also were of the opinion that it was impossible to arrive at constant results by Arneth's method and they evolved a method, termed the polymorphonuclear count. This is a simpler classification than that of Arneth. The polymorphonuclear neutrophil with an undivided nucleus is placed in their Class 1; in Class 2 is placed the cell whose nucleus has divided into two lobes; in Class 3 the cell with three lobes; and so on to Class 5. They state that the difficulty lies in determining whether or not the nucleus has divided; that the polymorphonuclear nucleus never divides completely; that there is always a fine filament of nuclear material uniting the different lobes. Therefore, as the basis of differentiating the five classes, Cooke's criterion is as follows: "If there is any band of nuclear material except this chromatin filament connecting the different parts of a nucleus, that nucleus cannot, for the purposes of the count, be said to be divided." They illustrate diagrammatically (see Fig. 1). The different groups of Cooke and Ponder are made plain by Fig. 2.

FIG. 1.—Scheme of Cooke and Ponder, illustrating Cooke's criterion. "If there is any band of nuclear material except a fine filament of nuclear material connecting the different parts of a nucleus, that nucleus for the purposes of the count cannot be said to be divided." (From "The Polynuclear Count," by Cooke and Ponder, London, Charles Griffin & Co., 42 Drury Lane, 1927.)

AUTHORS' WORK. The classification of the different types of polymorphonuclear neutrophils which we have attempted, is based upon the work of Arneth, Schilling, Piney, Pons and Krumbhaar, and more directly upon that of Cooke and Ponder. It appears that the differential estimation of the variations in the appearance of the nuclei of the neutrophils is a more delicate indication of infection than the ordinary total and differential count. Our attempt is to popularize a valuable method by further simplification, thus making it available for those lacking special training in blood examinations. It is our feeling that whenever and wherever a differential leukocyte count is made, the percentage of the different types of polymorphonuclear leukocytes should be determined.

In reviewing the work of Arneth, Schilling, and Cooke and Ponder, it seems that the classification of Arneth is too complicated for ordinary use, and that the method of Schilling lacks the clear-cut differentiation of cell nuclei which can be attained by following Cooke's criterion. The valuable classification of Cooke and Ponder can be simplified for the ordinary worker by dividing their five

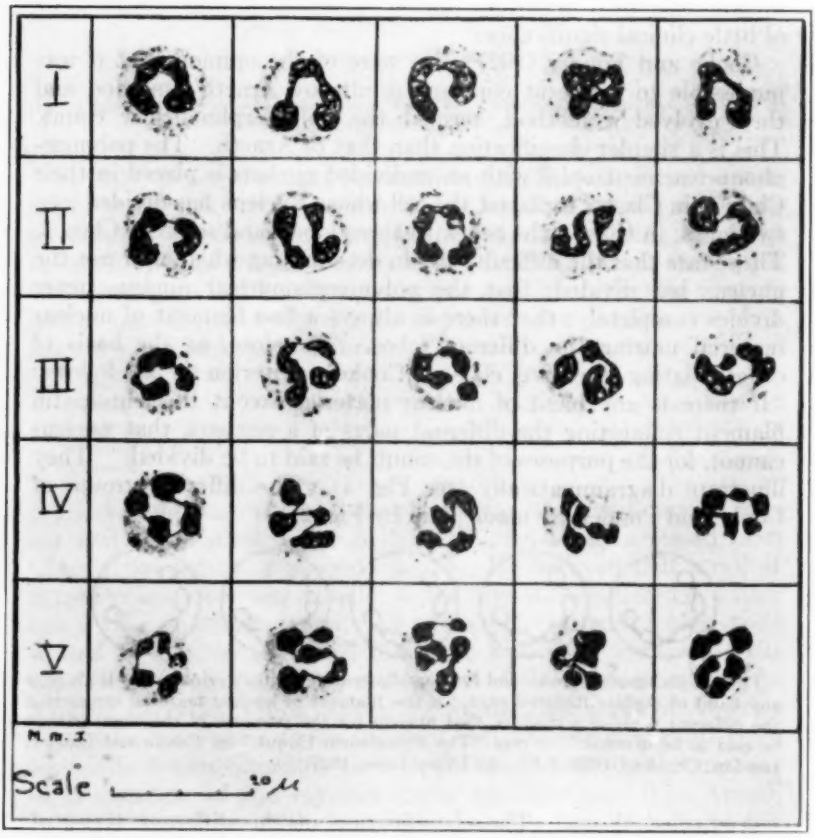


FIG. 2.—The five classes in the polynuclear count of Cooke and Ponder. If there is any band of nuclear tissue except a chromatin filament, uniting the nuclear masses, those parts must not be considered as separate segments. (From "The Polynuclear Count," by Cooke and Ponder, London, Charles Griffin & Co., 42 Drury Lane, 1927.)

classes into two classes, the first class to be identical with their Class 1, and the second class to include their Classes 2, 3, 4 and 5. Cooke's criterion serves for our purposes, thus to divide the polymorphonuclear neutrophils into two classes, "nonfilament" neutrophils and "filament" neutrophils. Distinct myelocytes or myeloblasts are to be counted as such. This is similar to the method of

Pons and Krumbhaar, except that their infrequent group of the metamyelocyte is here included in the nonfilament form. Cooke and Ponder have shown that the percentage of error in their classification when 50 neutrophils are counted is +0.09 and a satisfactory count can be obtained when as few as 50 cells are counted. We have adopted, therefore, the ordinary differential count where 100 cells are counted, as the basis of our work. Stated in simple terms, our count is the differentiation of 100 consecutive leukocytes to determine the percentage of nonfilament neutrophils, filament neutrophils, lymphocytes, monocytes, eosinophils and basophils, in which differential count, Cooke's criterion is used to separate the polymorphonuclear neutrophils into two groups. On this basis, we have attempted to establish a normal nonfilament and filament count in two ways: (1) By mathematics we have reduced the excellent normal chart of Cooke and Ponder; (2) by an actual series of counts on 100 normal individuals, we have attempted to find out especially the upper limit of the normal nonfilament count as well as the average nonfilament count. The upper limit of a normal is sometimes of more practical value than an average.

Reduction of the Normal Counts of Cooke and Ponder. Cooke and Ponder determined the normal polymorphonuclear neutrophil count in man and the extent to which it varied in health by taking the counts for ninety normal persons, each of whom was examined carefully to exclude infection. Their figures are based on counts of 100 neutrophils. By taking 70 per cent of the figures for Class 1, we have reduced their counts to the basis of 70, the usually accepted high normal neutrophil count in an ordinary differential leukocyte count where a total of 100 cells are counted, including leukocytes of all types. Their figures then become:

TABLE I.—TRANSFORMED NORMAL COUNTS OF COOKE AND PONDER.

No.	Nonfilament (%).	No.	Nonfilament (%).	No.	Nonfilament (%).	No.	Nonfilament (%).	No.	Nonfilament (%).	No.	Nonfilament (%).
1	7	16	6	31	9	46	5	61	7	76	6
2	9	17	11	32	9	47	4	62	4	77	9
3	11	18	10	33	7	48	6	63	6	78	5
4	6	19	13	34	7	49	7	64	8	79	5
5	8	20	11	35	5	50	7	65	3	80	7
6	5	21	11	36	5	51	4	66	5	81	4
7	9	22	5	37	7	52	11	67	8	82	5
8	5	23	9	38	2	53	6	68	6	83	2
9	6	24	5	39	9	54	5	69	7	84	7
10	5	25	9	40	8	55	8	70	8	85	4
11	12	26	5	41	7	56	8	71	6	86	7
12	4	27	9	42	5	57	7	72	7	87	5
13	12	28	11	43	4	58	8	73	5	88	8
14	10	29	3	44	3	59	5	74	5	89	8
15	3	30	12	45	5	60	7	75	5	90	4

The average count in 90 individuals is 6.08 cells.

Authors' Normal Counts. *Technique.* After comparing a number of special stains with the ordinary Wright's modification of the Romanowsky stain, we are convinced that excellent results can be obtained with the Wright stain and have used it throughout in our work because of its universal popularity. It is to be emphasized, however, that cover-slip preparations are to be used. We have found blood smears upon the ordinary microscopic slide unsuitable for accurate differentiation between filament and nonfilament neutrophils. The smears must be thin in order to have clear distinction of the nucleus. Thick smears make accurate differentiation impossible. We have taken the counts of 100 normal adults as follows:

TABLE II.—AUTHORS' NORMALS (100 CASES).

No.	Non-filament (%).	No.	Non-filament (%).	No.	Non-filament (%).	No.	Non-filament (%).	No.	Non-filament (%).
1	14	21	12	41	7	61	6	81	8
2	10	22	14	42	7	62	4	82	9
3	11	23	13	43	9	63	5	83	10
4	5	24	9	44	5	64	4	84	6
5	9	25	9	45	12	65	5	85	6
6	14	26	12	46	13	66	3	86	14
7	15	27	10	47	9	67	16	87	9
8	12	28	12	48	3	68	8	88	16
9	13	29	10	49	6	69	6	89	14
10	16	30	7	50	13	70	7	90	12
11	10	31	13	51	13	71	3	91	12
12	11	32	6	52	5	72	12	92	14
13	5	33	11	53	4	73	9	93	10
14	5	34	9	54	8	74	7	94	7
15	13	35	8	55	10	75	8	95	12
16	14	36	14	56	15	76	7	96	8
17	13	37	9	57	8	77	11	97	6
18	10	38	6	58	7	78	6	98	7
19	10	39	7	59	5	79	8	99	11
20	9	40	8	60	3	80	8	100	6

The average count in 100 individuals is 9.2 cells.

The test of a given clinical procedure is often the ease of its application divided by its usefulness. There seems little doubt that the estimation of the young forms of polymorphonuclear leukocytes gives valuable information. It is surprising how universally this conclusion is reached by practically all who have worked in this field. There seems to be, however, no easy method of making such a count and when one attempts to find normal standards, difficulties arise. We have attempted to find out the average normal young polymorphonuclear count (nonfilament forms) and especially the upper limit of the normal count. From our work we believe that 16 per cent can be used to practical advantage as the upper limit in health of normal young polymorphonuclear leukocytes (non-

filament forms) counted as outlined in this article. It is understood, of course, that this figure is somewhat arbitrary, but we have found such a definite figure of considerable practical value. For example, it often becomes necessary to decide whether a patient is merely neurotic and suffering from psychic, anxiety, or exhaustion pains, or whether there is in fact a hidden focus of disease. In such a case, if the young polymorphonuclear leukocytes number more than 16 per cent, we may become more assiduous in searching for the cryptic infection. Negative results, that is, a figure less than 16 per cent, we believe should be regarded as suggestive but not conclusive that the patient has no infection.

The method suggested is not intended to take the place of the more elaborate methods of Cooke and Ponder, Arneth, and others, but is designed especially for routine use. The great majority of blood counts are made by hospital resident physicians. It will be found to entail practically no additional labor in the ordinary differential count if the filament and nonfilament forms of polymorphonuclear neutrophils are estimated. We have found, indeed, that when once such a method is taught to an individual, his curiosity impels him to make such a division of the polymorphonuclears.

Cryptic infections, and cases where the patient may or may not be sick, appear to be the instances where the count is of most value. It would seem that except in unusual instances, the count is of no more value in prognosis than is the degree of temperature reaction. It indicates that the bone-marrow is active or inactive. A trivial infection may cause a marked reaction and *vice versa*. It is interesting to see the great increase in young forms in some cases where there is no hint of abnormality in the ordinary total and differential count. This is seen in those cases of overwhelming infection with normal counts or leukopenia. Patients with lobar pneumonia may have 60 per cent or more young forms without leukocytosis, a hidden picture, unless a young polymorphonuclear leukocyte count be made.

In Table III, we have itemized a few cases where the total and differential count gave an inadequate conception of the bone marrow activity, but where the nonfilament count indicated infection. This was especially noticeable in the cases of chronic pelvic inflammatory disease where usually the temperature also was normal. We compared a number of such cases with simultaneous sedimentation of red-cell estimation. The method of filament and nonfilament counting compared favorably with the sedimentation test. No elaborate comparison was made, but our general impression was that when the sedimentation test was abnormal there was usually an increase in the percentage of nonfilament forms above 16 per cent. These cases were checked by sections made from material removed at subsequent operation.

TABLE III.

	Total white blood cells.	Non-filament poly-morpho-nuclears.	Filament poly-morpho-nuclears.	Lymph-ocytes.	Mono-cytes.	Eosino-phils.	Baso-phils.
1. Pelvic phlebitis	6,200	50	38	2	8	0	0*
2. Pulmonary tuberculosis	6,000	21	42	15	21	1	0
3. Maxillary sinusitis	10,200	22	44	19	13	2	0
4. Acute mastoiditis	7,600	22	55	13	10	0	0
5. Lobar pneumonia	6,800	64	27	5	4	0	0*
6. Pulmonary tuberculosis	7,600	32	47	1	18	2	0
7. Acute sinusitis	9,100	34	37	11	18	0	0
8. Lobar pneumonia	8,700	54	27	12	5	2	0*
9. Subacute hepatitis	10,200	22	31	35	7	4	1
10. Rheumatic fever	9,000	24	35	23	14	1	1
11. Phlebitis	10,200	21	35	26	18	1	0
12. Miliary tuberculosis	8,000	43	25	14	14	2	2*
13. Vincent's angina	7,900	26	26	23	18	0	0
14. Chronic salpingitis	9,900	22	34	33	8	3	0
15. Chronic salpingitis	8,800	25	68	5	2	0	0
16. Chronic salpingitis	6,100	22	54	15	9	0	0
17. Chronic salpingitis	6,900	18	43	26	13	0	0
18. Chronic appendicitis	10,100	28	53	13	6	0	0
19. Chronic salpingitis	10,000	22	54	12	11	0	1
20. Chronic salpingitis	9,300	38	46	15	0	1	0
21. Chronic salpingitis	8,100	25	35	29	10	1	0
22. Abscessed tooth	7,800	28	36	28	6	2	0

* Death.

We have also (Table IV), calculated to our method a group of cases published by Cooke and Ponder.

TABLE IV.

	Cooke and Ponder's grouping of counts in infective states.					Calculated to author's groups.	
	I.	II.	III.	IV.	V.	Non-filament.	Filament.
1. Typhoid fever	54	31	15	0	0	38	32
2. Scarlet fever	44	43	13	0	0	31	39
3. Measles	45	39	16	0	0	31	38
4. Erysipelas	45	40	14	1	0	31	38
5. Diphtheria	41	39	17	3	0	29	41
6. Rubella	30	35	32	3	0	21	49
7. Variola	33	35	28	4	0	23	47
8. Pertussis	34	39	27	0	0	24	46
9. Puerperal sepsis	42	37	21	0	0	29	41
10. Gonorrhea	20	31	40	8	1	14	56
11. Acute poliomyelitis	39	27	27	7	0	27	43
12. Dental sepsis	26	38	30	6	0	18	52
13. Cerebrospinal fever	40	45	14	1	0	28	42
14. Septicemia	64	36	0	0	0	45	25
15. Osteomyelitis	47	41	12	0	0	33	37
16. Chronic nasal catarrh	28	31	37	4	0	20	50
17. Lobar pneumonia	57	26	15	2	1	40	30
18. Chronic bronchitis	25	45	23	7	0	18	52
19. Pulmonary tuberculosis	34	44	18	4	0	24	46

In Table V are a few of our own counts showing the relative number of young and old forms by our method where there was an increased number of total leukocytes:

TABLE V.

	Total white blood cells.	Non-filament poly-morpho-nuclears.	Filament poly-morpho-nuclears.	Lymph-ocytes.	Mono-cytes.	Eosino-phils.	Baso-phils.
1. Streptococcic septicemia .	18,000	51	15	15	19	0	0
2. Acute rheumatic fever .	12,100	21	35	26	18	0	0
3. Acute arsenical dermatitis	14,200	35	53	7	5	0	0
4. Lobar pneumonia . . .	61,000	59	37	3	1	0	0
5. Acute hepatitis . . .	14,400	45	7	33	14	0	1
6. Lobar pneumonia . . .	27,800	60	28	10	2	0	0
7. Lobar pneumonia . . .	15,900	39	38	20	4	0	0
8. Subacute sinusitis . .	12,200	22	44	19	13	2	0
9. Lobar pneumonia . . .	13,000	62	23	8	7	0	0
10. Lobar pneumonia . . .	14,100	80	10	7	3	0	0

The following brief history illustrates the value of the young polymorphonuclear leukocyte count in focal infections: Mrs. H. was admitted to the hospital suffering from a severe incapacitating sciatic neuritis. Roentgen ray films were made of the vertebrae, the pelvic bones, the teeth, and the nasal sinuses. Consultations were had with an orthopedic surgeon, a general surgeon, a dentist, a gynecologist, a specialist in diseases of the nose and throat, and an internist. The reports from these various examinations were entirely negative. The conviction that the patient had an area of focal infection which had been overlooked was strengthened by the fact that counts by three different individuals had shown nonfilament polymorphonuclear leukocytes of 31 per cent, 32 per cent and 34 per cent respectively. The total leukocyte counts were normal. The patient had no fever. Roentgen ray films accordingly were again made of the teeth. The report on the second examination was that a definite abscess was present at the apex of the first lower left molar tooth. This typifies many instances in which we have found the count of assistance in the diagnosis of cryptic infections. Had it not been for the definite increase in nonfilament forms, we would have concluded wrongly that the patient was suffering from a traumatic neuritis.

Summary. We believe that the most delicate method of studying the reaction of the bone marrow in infections of all types is the estimation of the young forms of polymorphonuclear neutrophils. This is in agreement with others. It is especially valuable in the diagnosis of cryptic infections of subacute or chronic types where there is no increase in the total leukocyte count. It may add additional presumptive evidence in cases of malingering and hysteria

masquerading as organic disease. Its value in prognosis is yet to be established. In profoundly toxic cases with a normal total count or a leukopenia, the agonized efforts of the bone marrow can be determined only by study of the character of the nucleus of the leukocyte.

Our method, stated briefly, is the differentiation of 100 consecutive leukocytes to determine thus the percentage of nonfilament neutrophils, filament neutrophils, lymphocytes, monocytes, eosinophils, and basophils, in which Cooke's criterion is used to separate the polymorphonuclear neutrophils into old and young groups. We wish to emphasize that this method is recommended especially for routine clinical examinations and not in competition with the more complex methods available to expert hematologists.

We have found by this method that the upper limit of a normal young polymorphonuclear leukocyte (nonfilament) count is in the neighborhood of 16 per cent of cells. The average count in 190 presumably normal adults was approximately 8 per cent. An increased percentage of young polymorphonuclear leukocytes may indicate the existence of infection, even though the total number of leukocytes is not increased.

REFERENCES.

Arneth, J.: Die neutrophilen weissen Blutkörperchen bei Infektionskrankheiten, Gustav Fischer, Jena, 1904.

Cooke, W. E., and Ponder, E.: The Polynuclear Count, Charles Griffin & Co., London, 1927.

Piney, A.: Recent Advances in Hematology, P. Blakiston's Son & Co., Philadelphia, 1928.

Pons, C., and Krumbhaar, E. B.: Studies in Blood Cell Morphology and Function; Extreme Neutrophilic Leukocytosis with a Note on a Simplified Arneth Count, J. Lab. and Clin. Med., 1924, **10**, 1.

Schilling, V.: Das Blutbild und seine klinische Verwertung, Gustav Fischer, Jena, 1926; also Ztschr. f. klin. Med., 1920, **89**, 1.

NOTE ON THE DIAGNOSIS OF PNEUMOCOCCUS PERITONITIS FROM THE BLOOD PICTURE.

By Charles L. Gibson, M.D.,

SURGEON TO THE FIRST SURGICAL (CORNELL MEDICAL) DIVISION OF THE NEW YORK HOSPITAL, NEW YORK.

The behavior of the differential blood count in pneumococcus peritonitis is so characteristic that the diagnosis of this condition can be made or suspected in practically all cases. I have already called attention to this blood count in a paper on pneumococcus peritonitis; but repeat it under a special heading to draw the attention of the profession more specifically to its important diagnostic side and to include two supporting examples.

I reproduce here a tabulation of the blood count in eight cases (Chart I).[1]

To emphasize the contrast in nonpneumococcic forms of peritonitis, particularly appendiceal peritonitis, the leukocyte-polymorphonuclear ratio in a group of fatal cases is exhibited (Chart II).

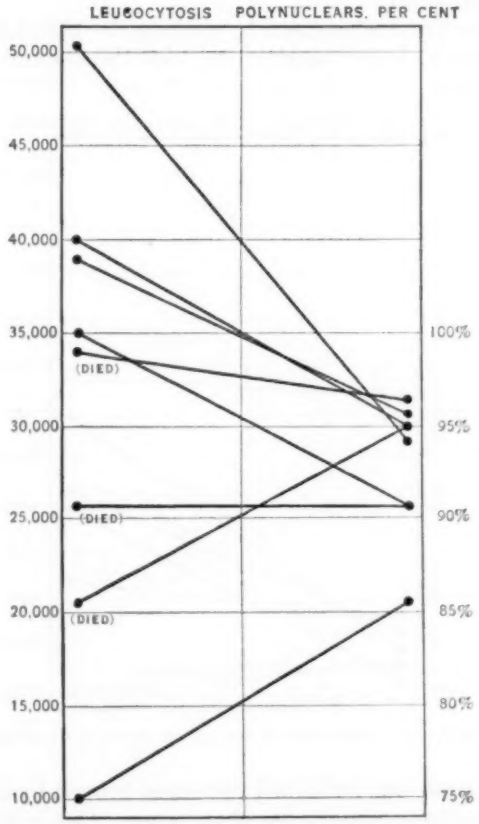


CHART I.—Eight cases of pneumococcic peritonitis.

Contrary perhaps to the general impression, the severe forms of ordinary peritonitis have relatively low leukocytosis with a fairly high polymorphonuclear per cent, whereas in pneumococcus peritonitis we have for the most part an extraordinarily high leukocytosis, as high as 74,000, with a high percentage of polymorphonuclears.

These blood counts are plotted on my so-called "Standard Chart"[2] where we start a baseline of 10,000 leukocytes, balanced by 75 per cent polymorphonuclears; the maximum normal count.

The differential count shows the tendency of the appendiceal peritonitis to start low down on the chart on the leukocyte side and rise toward the polymorphonuclear, whereas in pneumococcus peritonitis we start high up on the chart on the leukocyte side with a distinct drop toward the polymorphonuclears, which meet approximately at the same point as the ordinary appendiceal peritonitis, say 90 per cent or over.

This is a reaction that is given by nothing else that I know of and, as I repeat again, is so characteristic that the diagnosis should be at once obvious.

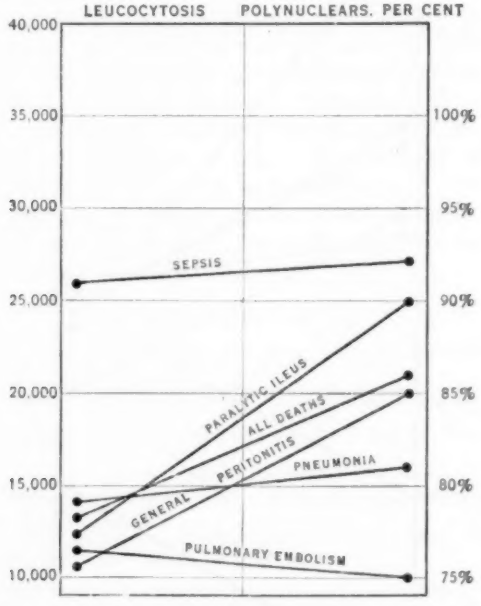


CHART II.—Five cases of nonpneumococcic peritonitis.

Since my paper was published two cases, proved by cultures, (the only criterion) have come under observation. One is in a boy, with secondary pneumococcus peritonitis, subsequent to a respiratory infection. This boy was not operated on, as, the diagnosis having been established, we knew there was no use operating on secondary forms, the only form seen in males. The patient recovered completely. The leukocytosis, 74,000, is the highest we have ever seen (Chart III).

The next case, in a female, making nine cases of primary pneumococcus infection studied, was seen recently in consultation. By primary pneumococcus peritonitis we mean that form of peritonitis where the portal of entry is through the genital tract and of course is seen only in the female, more usually in girls from four to seven

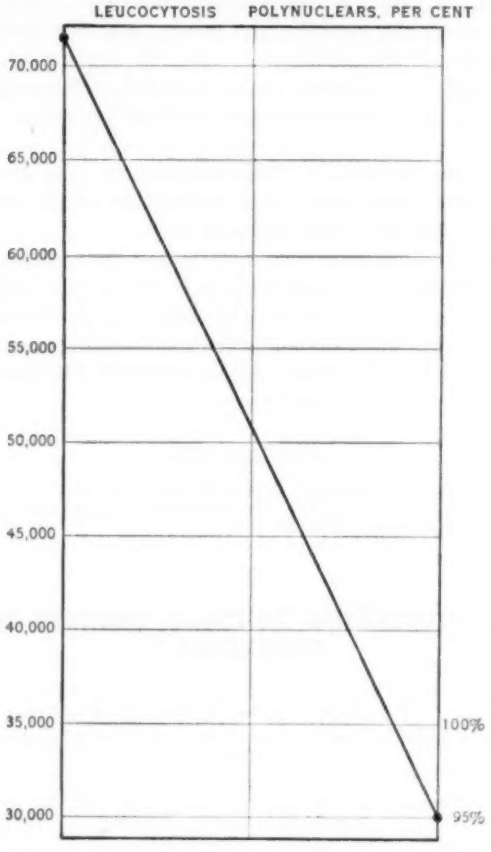


CHART III.—Pneumococcic peritonitis secondary to respiratory infection.

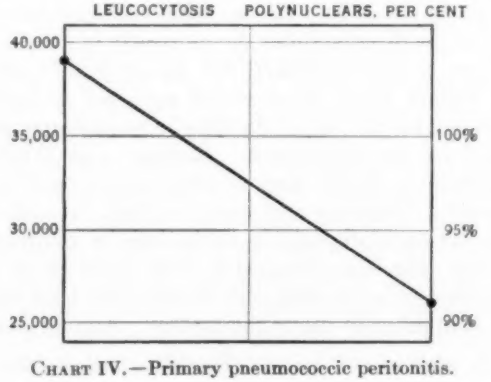


CHART IV.—Primary pneumococcic peritonitis.

years of age. A glance at the temperature chart, which showed an irregular temperature running for weeks, and the first differential count, namely 39,000 leukocytes and 92 per cent polymorphonuclears (Chart IV), allowed me to establish without hesitancy the diagnosis of primary pneumococcus peritonitis, which was verified at operation.

Pneumococcus peritonitis, while uncommon, is by no means rare, and can be easily recognized with realization of the significance of this absolutely characteristic blood picture.

Summary. In pneumococcic peritonitis the characteristic picture of an extraordinarily high leukocyte count with high percentage of polymorphonuclears is a valuable point in differential diagnosis from appendiceal and other nonpneumococcic forms of peritonitis.

In "Standard Blood Charts" this is brought out by a descending rather than an ascending curve.

BIBLIOGRAPHY.

1. Gibson, C. L.: Pneumococcus Peritonitis, 1925, **43**, 22.
2. Gibson, C. L.: The Value of the Differential Leukocyte Count in Acute Surgical Disease, Ann. Surg., 1906, **43**, 485.

STUDIES CONCERNING DIGITALIS THERAPY IN LOBAR PNEUMONIA.*

By Walter L. Niles, M.D.,

PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE, NEW YORK CITY.

AND

John Wyckoff, M.D.,

ASSOCIATE PROFESSOR OF MEDICINE, NEW YORK UNIVERSITY, NEW YORK CITY.

Although many authors have expressed opinions concerning the therapeutic value of digitalis in lobar pneumonia, review of the literature fails to reveal any studies which present definite evidence that the use of the drug modifies the mortality of the disease. While a few observers, notably Carhart,[1] Sir James Mackenzie,[2] Brunton,[3] Hare,[4] and Stuart Hart[5] have either opposed or have expressed little enthusiasm for the use of digitalis in pneumonia, most authors have favored its administration. Burrage and White,[6] in 1927, studied the records of 221 cases of lobar pneumonia in the Massachusetts General Hospital and reported that no untoward effects from a toxic action of digitalis in their series were observed. They concluded that the data suggested that digitalis is of value in pneumonia when given in sufficient dosage, but that the cases were inadequate in number to prove the matter. Among those who have

* Read at the Association of American Physicians, Atlantic City, N. J., May 5, 1930.

advocated the routine use of digitalis in pneumonia are Stone, Phillips and Bliss,[7] who studied records of the U. S. Army Base Hospital at Fort Riley, Kansas. Stone[8] subsequently analyzed the records in greater detail and added to the number of digitalis treated cases, as the result of which he advanced data favoring the beneficial effects of digitalis in the pneumonias without sepsis. Brooks and Carroll[9] analyzed 5000 protocols of cases dying in the American Expeditionary Forces in France and concluded that routine digitalization was beneficial in the older age groups. In neither of these series was there an unselected group of untreated controls observed simultaneously with and under identical circumstances as the digitalis-treated cases. A group of control cases is of course essential for sound conclusions. The analysis of hospital records of previous years with the division of cases into digitalis untreated and treated groups does not constitute a properly controlled series, for as a rule, under these circumstances the milder cases receive no digitalis, while the more severe cases are thought to need and are given digitalis. This fact is well brought out by Randolph[10] in his analysis of 100 consecutive cases at the George Washington University Hospital and by Cohn and Jamieson[11] in their study of 105 cases at the Hospital of the Rockefeller Institute, and also by Burrage and White[6] in their analysis of cases at the Massachusetts General Hospital. The method of Hart, in his study of influenzal pneumonia in which a considerable number were selected at random from time to time, does not satisfy one. Neither does the comparison of untreated cases observed during one period of time with cases treated with digitalis during another period seem justified, as was done by Stone, Phillips and Bliss, and later again by Stone, when the virulence of the infecting organisms admittedly differs from time to time.

The observation that digitalis failed to slow the heart in fevers led many clinicians to doubt if it produced any effect in pneumonia. In 1917 Cohn and Jamieson demonstrated that the drug produced in the pneumonia heart the same electrocardiographic changes that were found in normal controls. Cohn[12] had concluded in 1916 "that digitalis did not harm and it might be life saving" and reported that, therefore, digitalis was given to all pneumonia patients at the Hospital of the Rockefeller Institute as a routine. Since that time it has been widely used in pneumonia, and has generally been given as a routine on the three Medical Divisions of Columbia University, Cornell University and New York University at Bellevue Hospital. The attending physicians, however, were doubtful of its effect on the mortality rate and believing that unusual opportunities for further study were available at Bellevue Hospital, in 1927 formed a committee (*a*) to organize and supervise a study of the effects of digitalis in pneumonia. The observations were carried on continuously throughout the years 1928 and 1929 and are the basis for this report.

The University services at Bellevue Hospital were believed to present unusual advantages for such a study: (1) For the reason that a large number of cases could be observed; (2) for several years cases of lobar pneumonia had been treated with specific antipneumococcus serum on a carefully controlled plan with untreated control cases equal in number to those treated, and (3) because interest and study in the use of digitalis in heart disease has been a tradition on these services for fifty years.

In accordance with the plan already in operation, patients were admitted into the pneumonia series according to the date and hour of admission, alternate cases being treated with serum. The combination of serum and digitalis therapy led to the grouping of these patients into four classes, selected only by the time of admission, and were designated Classes A, B, C and D, two of which were controls and two treated, with reference to each type of treatment. Thus:

Class A received neither serum nor digitalis.
Class B received serum only.
Class C received digitalis only.
Class D received both serum and digitalis.

This system of classification operated on each ward independent of other wards so that factors of general care and nursing might be the same for each class of treatment.

During the first year of the digitalis study all cases of lobar pneumonia were included in the series regardless of the duration of the disease or the presence of systemic complications. In the second year those who gave a history of more than eight days duration and those with general systemic diseases were excluded from the digitalis serum series.

Exactly similar observations were made on the control and on the treated patients. In addition to the usual clinical and laboratory examinations an electrocardiogram was made daily during the febrile period and on alternate days thereafter. A control record was made on all digitalis-treated patients before any digitalis was administered. In the first year, 2668 electrocardiograms were taken and in the second year 3369. Of the 835 cases studied in both years, 625 or over seven-tenths were electrocardiographed three or more times, about two-tenths had one or more tracings; 57, or less than one-tenth, died before any records could be obtained.

Precautions were taken to insure accurate administration of the digitalis at the time ordered. The digitalizing dose of each patient was put in a small cardboard box by the physician in charge, labeled with his or her name and given to the nurse in charge of the ward. The order for digitalis was written in the ward order book and also on a manilla tag which was fastened to the patient's bed. When the nurse gave the digitalis she initialed the tag and noted the hour. These tags were collected later and constitute a permanent record.

In addition to the regular professional staff, a full-time Fellow (*b*) was assigned to supervise the digitalis treatment. He was assisted by an electrocardiographic technician and a diener. Another full-time Fellow gave the serum treatment and was in charge of the bacteriological work.

Upon beginning the study it was decided to continue to employ on each Medical Division that preparation of digitalis which had previously been in routine use, namely, one commercial preparation, termed Specimen B, on the First and Second (Columbia and Cornell) Divisions, and another commercial preparation, termed Specimen A, on the Third (New York University) Division. Both preparations had been standardized by the manufacturers by the cat method of Hatcher. Specimen A was reported to have a potency of 100 mg., equivalent to one cat unit; the other, Specimen B, of 66 mg., equivalent to one cat unit. Having been in routine use in the wards there was at that time no reason to doubt the reliability of their standardization. However, it was later noted that there was a high incidence of toxic signs in patients treated with the B preparation, and it was subsequently found that this specimen of digitalis was approximately twice as active as the manufacturer had stated in terms of cat-unit potency. A preliminary report[13] dealing with the standardization of this preparation has been published, and a more detailed article is in the hands of the publishers. When the error in standardization had been proved, a third, non-commercial, standardized preparation of digitalis was used, and was administered on all the divisions.

It was realized that in an acute disease like pneumonia the patients should receive their digitalis rapidly. At the same time it was felt that the production of toxic effects should be prevented if possible. For this reason it was decided to give the digitalis in divided dosage and in no case to give a patient a digitalizing dose of more than 0.15 of a cat unit per pound of body weight, and to stop the administration of the drug before this amount was given if toxic symptoms were observed. During the first year the dose was divided into parts approximating 30 per cent, 30 per cent, 15 per cent, 15 per cent and 10 per cent of the estimated dose and these were given at intervals of six hours, the last dose (when given) being given about twenty-four hours after the first. As it was deemed unwise and unnecessary to weigh the patients, they were divided roughly into three groups: those who appeared to weigh less than 125 pounds, those weighing between 125 and 175 pounds and those weighing over 175 pounds.

Because of the incidence of toxic signs, especially vomiting and the higher grades of heart block, in the digitalis-treated cases, it was decided in the second year of the investigation to reduce the dosage to nearly half. Patients were then divided into two weight groups instead of three, namely, above and below 150 pounds. The

lighter weight group received a total digitalizing dose of 10 cat units, or 1 gm., and the heavier, of 12.5 cat units, or 1.25 gm. This was administered in three doses, the first, 50 per cent of the total, the second 25 per cent given twelve to eighteen hours after the first, and the third dose, 25 per cent, given after another interval of six to eight hours.

A daily maintenance dose of 2 cat units was given in both years. This was administered in a single dose each morning, and was discontinued when the temperature became normal or when toxic signs developed.

The data which were collected during the two-year period of this investigation have been studied recently. We will present at this time a summary of the results according to the factors which are known materially to affect the mortality rate in lobar pneumonia, namely: sex, age, pneumococcus type and the severity of the infection as indicated by septic complications and positive blood cultures. More detailed studies will be published subsequently.

TABLE I.—COMPARATIVE MORTALITY OF DIGITALIS CONTROL AND TREATED CASES FOR THE FIRST AND SECOND YEARS OF THE INVESTIGATION.

	Digitalis control.			Digitalis-treated.			Difference in mortality, per cent.
Year	No. of cases.	No. died.	Mortality, per cent.	No. of cases.	No. died.	Mortality, per cent.	
First . . .	197	68	34.5	158	67	42.4	7.9
Second . . .	207	68	32.9	180	73	40.6	7.7
First and second	404	136	33.7	338	140	41.4	7.7

Table I shows that although the mortality rate was slightly higher in both the control group and the digitalis-treated group in the first year of the study the differences in the mortality rate for both years were remarkably similar. It indicates that for every 100 cases in the control group that died there were 122 fatalities in the digitalis-treated group.

TABLE II.—COMPARATIVE MORTALITY OF PATIENTS RECEIVING DIGITALIS A, B AND G AND OF CONTROL PATIENTS.

Digitalis.	No. of cases.	No. died.	Mortality, per cent.
A	90	33	36.7
B	142	67	42.2
G	106	40	37.7
Controls	404	136	33.7

Table II shows the number of cases and the mortality according to the preparation of digitalis which was given. As stated above, due to erroneous standardization of Specimen B, patients treated with this preparation received approximately twice the estimated dose calculated by the body-weight method. Specimen A was administered in the correct dosage. Specimen G was given entirely in the smaller dosage, approximately one-half of the total digitalizing dose as calculated by the body-weight method.

It may be seen in Table II that the percentage mortality of the cases treated with Specimen B is 13.5 higher than of the control group. Or it may be stated that for every 100 control patients that died there died 140 patients treated with Specimen B. The differences in percentage mortality between cases treated with Specimen A and G and the control group is only 3.0 and 4.0 respectively.

Specimen B was administered to 63 per cent of all digitalis-treated cases in the first year and to only 30 per cent of all digitalis-treated cases in the second year; also the group which was given Specimen G received much smaller doses as described before. It is therefore of interest to recall Table I, which gives comparisons with the control group in each year. It showed that the difference in percentage mortality is practically the same in each year. Therefore one may conclude that over-dosage with digitalis is not the sole cause for the higher mortality rate of the digitalis-treated group.

TABLE III.—MORTALITY OF MALES AND FEMALES FOR DIGITALIS CONTROL AND TREATED PATIENTS.

	Digitalis control.			Digitalis-treated.			Difference in mortality, per cent.
Sex.	No. of cases.	No. died.	Mortality, per cent.	No. of cases.	No. died.	Mortality, per cent.	
Male . . .	357	123	34.5	299	125	41.8	7.3
Female . .	47	13	27.7	39	15	38.5	10.8

Table III deals with the factor of sex and shows that the mortality rate is higher for both sexes in the digitalis-treated groups as compared with that of the controls. The difference in mortality shown in Table I cannot, therefore, be due to a preponderance of males, which sex always gives a higher mortality than do females.

TABLE IV.—MORTALITY OF AGE GROUPS FOR DIGITALIS CONTROL AND TREATED PATIENTS.

	Digitalis control.			Digitalis-treated.			Difference in mortality, per cent.
Age group in years.	No. of cases.	No. died.	Mortality, per cent.	No. of cases.	No. died.	Mortality, per cent.	
10 to 29 . .	94	15	16.0	73	19	26.0	10.0
30 to 39 . .	109	30	27.5	76	25	32.9	5.4
40 to 49 . .	99	40	40.4	99	44	44.4	4.0
50 plus . .	102	51	50.0	90	52	57.8	7.8
Totals . .	404	136	33.7	338	140	41.4	7.7

Age is well known to influence mortality in pneumonia, the older groups showing a higher death rate than the younger groups. Table IV shows that the mortality of the digitalis-treated cases is higher than that of the corresponding controls in both the older and the younger groups. Therefore, a preponderance of old patients in the digitalis-treated group is not an explanation for the higher mortality rate in the treated cases shown in Table I.

TABLE V.—MORTALITY OF PNEUMOCOCCUS TYPES FOR DIGITALIS CONTROL AND TREATED CASES.

Type.	Digitalis control. No. of cases.	Digitalis control. No. died.	Digitalis control. Mortality, per cent.	Digitalis-treated. No. of cases.	Digitalis-treated. No. died.	Digitalis-treated. Mortality, per cent.	Difference in mortality, per cent.
I	98	22	22.4	66	23	34.8	12.4
II	130	62	47.7	108	49	45.4	−2.3
III	28	9	32.1	25	12	48.0	15.9
IV to XIII and unclassified	135	33	24.4	128	50	39.1	14.7
Miscellaneous	13	10	....	11	6		
Totals	404	136	33.7	338	140	41.4	7.7

Table V analyzes the factor introduced by variation in the virulence of the specific pneumococcus types. It shows that in all types, except Type II, the mortality of the digitalis-treated cases is higher than that of their controls.

TABLE VI.—MORTALITY OF PNEUMOCOCCUS TYPES BY AGE GROUPS FOR DIGITALIS CONTROL AND TREATED GROUPS.

Type.	Age in years.	Digitalis control. No. of cases.	Digitalis control. No. died.	Digitalis control. Mortality, per cent.	Digitalis-treated. No. of cases.	Digitalis-treated. No. died.	Digitalis-treated. Mortality, per cent.	Difference in mortality, per cent.
I	10 to 39	62	6	9.7	33	6	18.2	8.5
	40 plus	36	16	44.4	33	17	51.5	7.1
II	10 to 39	53	21	39.6	54	17	31.5	−8.1
	40 plus	77	41	53.2	60	36	60.0	6.8
III	10 to 39	11	1	9.1	9	4	44.4	35.3
	40 plus	17	8	47.1	16	8	50.0	2.9
IV to XIII and unclassified:								
	10 to 39	72	12	15.5	53	15	28.3	12.8
	40 plus	63	21	33.3	75	35	46.7	13.4

Table VI subdivides the pneumococcus types into younger and older-age groups. It reveals that the single exception regarding the higher mortality in the digitalis-treated cases is found in the younger age group with Type II pneumococcus infections. No explanation has been found for this exception. However, if all cases which were admitted to the series (not excluding cases discharged at their own risk, cases in the C and D series which received no digitalis, and deaths occurring within twenty-four hours after admission) are analyzed, we find that, in common with all other types, the mortality of the digitalis-treated group in Type II infections is higher than in the control group.

The factor of virulence may possibly be measured by the incidence of septic complications. Again this factor is found not to influence the relative mortality of the control and digitalis-treated cases.

It was suggested that if the cases with septic complications were excluded from the series a better comparison could be drawn of the mortality in the control and digitalis-treated cases. Table VIII

makes a comparison of the mortality rates of the presumably milder, uncomplicated cases, and the difference between the control and the treated groups is seen to persist.

TABLE VII.—MORTALITY OF CASES WITH SEPTIC COMPLICATIONS FOR DIGITALIS CONTROL AND TREATED GROUPS.

Pneumococcic complication.	Digitalis control.		Digitalis-treated.	
	No. of cases.	No. died.	No. of cases.	No. died.
Empyema	13	6	16	11
Endocarditis	1	1	1	1
Pericarditis	3	3	0	0
Meningitis	0	0	4	4
Arthritis, suppurative	0	0	2	2
Lung abscess	2	1	1	1
Otitis media, purulent	5	3	3	0
Totals	24	14	27	19
Mortality	58.3 per cent		70.4 per cent	
Difference in mortality	12.1 per cent			

TABLE VIII.—MORTALITY OF THE GENERAL SERIES EXCLUDING CASES WITH SEPTIC COMPLICATIONS FOR DIGITALIS CONTROL AND TREATED GROUPS.

Group.	Digitalis control.			Digitalis-treated.			Difference in mortality, per cent.
	No. of cases.	No. died.	Mortality, per cent.	No. of cases.	No. died.	Mortality, per cent.	
General Series	404	136	33.7	338	140	41.4	7.7
"Septic" cases	24	14	58.3	27	19	70.4	12.1
Series excluding "septic" cases	380	122	32.1	311	121	38.9	6.8

TABLE IX.—COMPARATIVE MORTALITY OF PATIENTS WITH NEGATIVE AND POSITIVE BLOOD CULTURES FOR DIGITALIS CONTROL AND TREATED GROUPS.

Blood culture.	Digitalis control.			Digitalis-treated.			Difference in mortality, per cent.
	No. of cases.	No. died.	Mortality, per cent.	No. of cases.	No. died.	Mortality, per cent.	
Positive	54	43	79.6	53	42	79.2	−0.4
Negative	124	25	20.2	116	40	34.5	14.3

It may be asserted that cases with frank septic complications do not truly represent all cases of so-called sepsis, such as septicemia in which no localization has occurred and that the cases with positive and those with negative blood cultures form a better basis for comparison. Table IX shows that in the most severe cases, those with positive blood cultures, there is no difference in the mortality rates between the control and digitalis-treated groups, while in the milder cases, with negative blood cultures the mortality is 14.3 per cent higher for the treated group.

TABLE X.—MORTALITY AND INCIDENCE OF AURICULAR FIBRILLATION AND FLUTTER.

Auricular fibrillation and flutter.	Digitalis control (429 cases).	Digitalis-treated (406 cases).	Total, all cases (835 cases).
Number of cases	17	16	33
Incidence in series	4.0 per cent	3.9 per cent	4.0 per cent
Number died	9	14	23
Mortality	52.9 per cent	87.5 per cent	69.7 per cent

Table X shows that the incidence of auricular fibrillation and auricular flutter is the same in the control and the digitalis-treated groups. The mortality is, however, distinctly higher in the digitalis-treated group. Although the number of cases is not sufficient to warrant drawing conclusions the inference is clear. These complications are now being subjected to further study and communications on this subject will be issued subsequently.

Conclusion. Although the Committee would prefer to continue the investigation on the results of digitalis therapy in pneumonia and observe a larger number of cases over a series of years, it was the unanimous opinion of the Committee and its advisers that the results obtained thus far do not justify continuing the routine administration of digitalis to patients suffering with lobar pneumonia.

(*a*). The committee for the study of digitalis in pneumonia is composed of Drs. Norrie and Woodruff of the First (Columbia University) Medical Division, Drs. Dubois, Niles and Eggleston of the Second (Cornell University) Medical Division, and Drs. Wyckoff and DeGraff of the Third (New York University) Medical Division of Bellevue Hospital.

(*b*). The Fellows in Medicine in charge of the digitalis investigation were Marjory Shearer, M.D., during the first year, and Janet G. Travell, M.D., during the second year. The authors desire to express their appreciation for the invaluable services rendered by these Fellows.

BIBLIOGRAPHY.

1. Carhart: J. Am. Med. Assn., 1891, **16**, 811.
2. Mackenzie: Diseases of the Heart, 2d ed., 1908.
3. Brunton: Therapeutics of the Circulation, 2d ed., London, 1914, p. 281.
4. Hare: Pneumonia: Handbook for Practical Treatment, 1911, **2**, 269.
5. Hart: Am. J. Med. Sci., 1919, **158**, 649.
6. Burrage and White: Am. J. Med. Sci., 1927, **174**, 260.
7. Stone, Phillips and Bliss: Arch. Int. Med., 1918, **22**, 409.
8. Stone: Am. J. Med. Sci., 1922, **163**, 659.
9. Brooks and Carroll: Am. J. Med. Sci., 1920, **160**, 815.
10. Randolph: Arch. Int. Med., 1929, **43**, 248.
11. Cohn and Jamieson: J. Exp. Med., 1917, **25**, 65.
12. Cohn: New York Med. J., 1917, **105**, 234.
13. Wyckoff and Gold: J. Am. Med. Assn., 1930, **94**, 626.

BARIUM CHLORID IN THE STOKES-ADAMS SYNDROME OF COMPLETE HEART BLOCK.

Negative Results in Eight Cases.

By Aaron E. Parsonnet, M.D.,

Newark, N. J.,

and

Albert S. Hyman, M.D.,

New York City.

Complete heart block with auricular and ventricular dissociation has always attracted the attention of clinicians. The peculiar physiologic phenomena occurring in this condition have been a constant source of further investigation both in the laboratory and

clinic. The factors involved in the development of independent auricular and ventricular rhythms have long been known; any process which prevents the excitation wave from completing its journey from the sinoauricular node through the auricular musculature to the auriculoventricular node of Tawara will permit the establishment of an independent ventricular rhythm. We have previously pointed out the life-saving mechanism which is involved in this interplay of the two pacemakers of the heart.[1]

Where the ventricular rhythm is regular and the rate averages from 36 or more beats per minute the patient may experience no especial difficulties, and if he lives within the functional capacity of his heart the condition may persist for many years. Mackenzie[2] watched several such cases for about twenty years. Harris[3] reported a case which lived for twenty-eight years; Willius[4] studied a case fifteen years after its original onset. Wells and Wiltshire's[5] patient had the condition for twelve years, and Lewis[6] saw a patient with complete heart block for fifteen years. Two cases under our observation have lived for eleven and eight years respectively.

On the other hand, where there are irregularities of rhythm and when the ventricular rate is so slow that the development of the Stokes-Adams syndrome is present or imminent a frantic search for remedies must be made, more especially if the seizures are frequent. The past decade has seen many modes of therapy recommended for the relief of this serious phase of complete heart block. Wenckebach showed that after a simple exercise test a complete heart block might be temporarily broken up; an increase in the circulation of the conducting system area of the heart was said to enhance the probability of conduction. In such cases Phear and Parkinson[7] demonstrated, in 1922, that adrenalin, injected either subcutaneously or intravenously, exerted a favorable effect upon the convulsive seizures due to the Stokes-Adams phenomenon. Prior to this, in 1916, Danielopolu[8] reported the experimental use of adrenalin for the relief of unconsciousness due to cerebral anemia from the slowly acting ventricle of complete heart block.

Whether adrenalin enhanced conductivity by increasing the circulation of the bundle system through vasodilatation of its intrinsic vessels as suggested by Cushny,[9] or whether it is due to stimulation of the sympathetic nerve endings in the auriculoventricular bundle with subsequent improvement of conductivity as maintained by Routier,[10] certain it is that adrenalin exerts a definite though brief action in this condition.

Atropin, when used in large doses, has in certain cases been apparently of value; where the Stokes-Adams syndrome is dependent upon overactivity of the vagus so that conductivity of the bundle system is inhibited the belladonna derivatives may prove to be a physiologic antidote. From a clinical point of view, however, little if any relief has been secured from this remedy. Herman and

Aschman,[11] in a study of atropin in complete heart block, have found it to be of slight symptomatic value for the relief of syncope even if there was an increased auricular rate.

Many other drugs from time to time have been suggested; thyroid gland substance or its chemical derivative, thyroxin, has recently been again urged in this condition. Drake[12] reported some success with the administration of this substance in a case of complete block with the Stokes-Adams syndrome. Blackford and Willius,[13] as long ago as 1917, reported favorable results obtained in 4 cases of this type treated by injections of thyroxin. Even digitalis, the use of which has been theoretically barred in any condition of depressed conductivity, has been shown by Erlanger[14] to be of value in cases of heart block due primarily to insufficient coronary circulation. Where congestive failure has rendered the junctional tissue relatively unresponsive, digitalis, by improving the nutritional state of the myocardium in general, can exert a benign influence.

Much controversial opinion has been expressed for and against numerous other incidental agents which have been reported from time to time in isolated instances; in view, however, of the unreliable results obtained from the more commonly used remedies already mentioned, this is unavoidable and the quest for a specific agent is still in progress. Apparently many drugs offer relief under certain ill-defined conditions occurring simultaneously with the Stokes-Adams syndrome as it is seen in complete heart block. The nitrites, theobromin, euphyllin, alpha-lobelin, cardiazol, coramin, camphor and even dextrose have been reported serviceable.

Finally, the salts of barium and calcium have been suggested. Based upon the well-known experimental work of Rothberger and Winterberg,[15] conducted on dogs and controlled by electrocardiographic studies, it was shown that both drugs increased the irritability of the cardiac muscle. In 1923 Wilson and Herman[16] reported the first clinical use of barium chlorid for the relief of the Stokes-Adams syndrome. Following this, Cohn and Levine[17] gave their experiences in 3 cases where barium chlorid was given by mouth. Levine subsequently collected 2 additional cases[18] and later a third[19] case which received adrenalin intracardially, together with barium chlorid by mouth.

The favorable results in these cases have been confirmed by others; Parsons-Smith,[20] Strauss and Meyer[21] and Price and Nisse[22] have obtained various degrees of success with barium chlorid. On the other hand, Heard, Marshall and Adams[23] were not favorably impressed by the action of barium chlorid in their patient.

The rationale of barium chlorid therapy for the prevention and relief of the Stokes-Adams syndrome that is due to complete heart block is based upon the increase in the irritability curve of the ventricle when the drug is given in sufficiently large doses. It has

also been shown that the degree of resistance offered to the excitation wave as it approaches the atrioventricular junction of the heart is decreased almost to the same extent as the increase in the irritability of the myocardium. These two factors, while producing the same ultimate effect, are concerned with two different functions of the heart. From a theoretic point of view, either of these processes if effective will permit previously blocked impulses to pass through from the auricle to the ventricle and would assure the reëstablishment of a normal auriculoventricular rhythm. On the other hand, when the irritability curve is increased the ventricles may go into such a state of sensitivity that ventricular fibrillation may develop. Such attacks of ventricular fibrillation have been reported from time to time. With this as its only contraindication, many authors have recommended barium chlorid for Stokes-Adams seizures.

We, however, have been unable to confirm the uniformly effective results of previous investigators. In the close scrutiny demanded of any new remedy, negative findings may often be of greater significance in the total estimation of therapeutic value than the occasional confirmatory reports. This holds true of any new therapeutic agent; Puckner and Leech[24] and Leake[25] have stressed this as one of the cardinal requisites in appraising an acceptable new remedy.

We have been interested in the use of barium in a series of 8 cases of complete heart block complicated by the Stokes-Adams syndrome. In none of these cases were we able to obtain any semblance of pharmacologic or physiologic action either good or bad. Special attention was focused upon the quality and the source of barium employed; through the courtesy of a pharmaceutical laboratory in Newark, N. J., a standard tablet containing 0.04 gm. of chemically pure barium chlorid was prepared. These tablets were readily soluble in water and conformed to the standard fragility tests.

Amounts varying from 0.04 to as much as 0.6 gm. were given in twenty-four hours; these doses were continued in various cases from one week to three months and electrocardiographic control of each case was made every two weeks to two months. Full coöperation of the patients was secured by informing them of the experimental character of this remedy, and they were instructed to report immediately upon the development of any new or unusual symptoms. In the period of over three years during which this study was continued only twenty-one emergency calls were made, most of which had no relation to the patients' cardiovascular condition. During the same period 2 patients have died, both of whom were subject to severe Stokes-Adams attacks and in whom there was extensive involvement of the coronary arteries.

A brief résumé of these 8 cases follows:

Case Reports. CASE I.—A. E., male, aged fifty-six years, baker, up to the age of fifty-two the patient had pursued an active and vigorous life. At that time he began to complain of stenocardia which prevented him from

continuing his occupation. The anginal seizures were at first easily controlled by the use of theobromin, but two years later the attacks had become very severe and rendered the patient bedfast. The attacks then disappeared and the patient was able to move cautiously around the house. While sitting in a chair one day he was seen to fall forward and dropped unconscious upon the floor; the family physician, on his arrival found that the patient had recovered consciousness but was still mentally confused. Physical examination at that time showed the pulse to be extremely slow, averaging from 26 to 32 beats per minute. The blood pressure was 100 systolic and 60 diastolic and the heart sounds were of very poor quality. During the next few months he had several such fainting spells, the last of which was so severe that the patient remained unconscious for almost an hour. On the following day he was referred to one of us for cardiovascular study.

Electrocardiographic examination (Fig. 1) revealed a complete auricular and ventricular dissociation; the ventricular rate was rather regular at 26 beats per minute, with an auricular rate of about 72. There were *T*-wave alterations in all leads suggesting considerable coronary artery involvement. There was no axial deviation of the heart but there were apparently two centers for the origin of the ventricular beat.

The general physical examination showed the typical change seen in advanced myocardial disease: the patient was dyspneic, his mucous membranes were cyanotic and he had the peculiar pallor so often seen in coronary disease. The heart was greatly enlarged and the cardiac impulse almost imperceptible. The liver was not enlarged but a slight pretibial edema was present. The Wassermann was negative.

A diagnosis of Stokes-Adams syndrome as a result of complete heart block was made and the patient was placed upon moderately large doses of euphyllin. The attacks continued to occur, however, with alarming regularity and after a six weeks' trial with this drug it was abandoned. Adrenalin was used frequently during the attacks with inconstant results; sometimes the patient could be restored to consciousness within half a minute, at other times 2 and even 3 injections were apparently without effect, the patient returning to consciousness spontaneously.

On October 10, 1928, the patient was first placed upon barium chlorid therapy. The standard tablets containing 0.04 gm. were given three times a day; this quantity was cautiously raised over a period of two weeks to two tablets every four hours for 6 doses, representing 0.32 gm. in twenty-four hours. This amount was then continued over a period of twenty-one days making a total of 8.48 gm. for the first month. During this time no effect directly attributable to the barium was noted. Electrocardiographic studies remained unchanged and clinically the patient continued to have his convulsive seizures. Treatment was then stopped for about ten days during which time the patient was taken to Lakewood, N. J. While there he had two severe attacks which so alarmed his relatives that he was promptly returned home. On close questioning it was found that these attacks were no more severe, perhaps, than those occurring while under barium therapy. The patient expressed the belief that barium seemed to help him so that he was again placed on 0.32 gm. per day. This amount he continued to take until March 3, 1929, a period of 126 days, during which 40.32 gm. of barium were taken altogether.

On that latter date he had an attack so severe that even an intracardiac injection of adrenalin failed to arouse him. His pulse at the wrist was imperceptible and the heart sounds were very weak and irregular at a rate estimated to be about eight or nine beats per minute. With the onset of pulmonary edema, vomiting took place and the patient promptly became conscious. He was now confined to bed with infrequent attacks for the next two

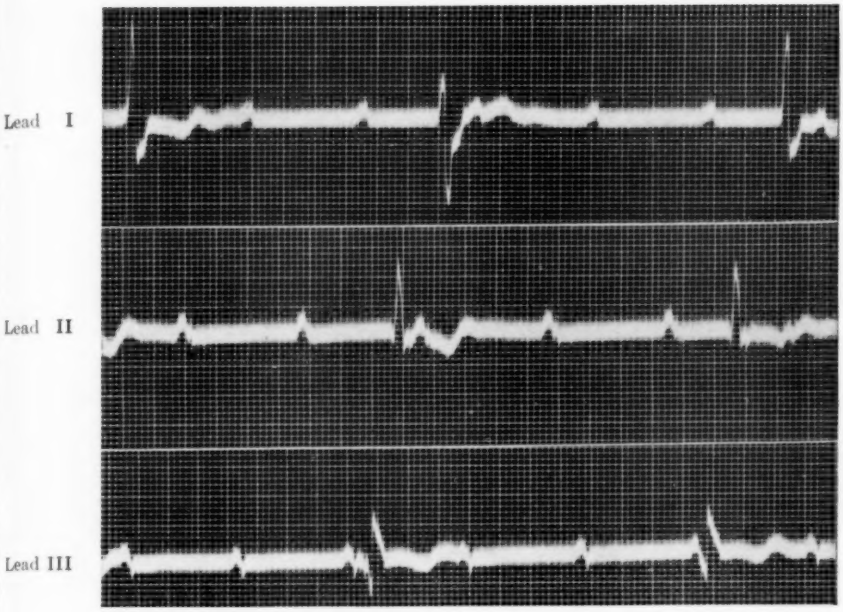


FIG. 1.—Complete heart block; in Lead I note accessory center of origin of the ventricular beat.

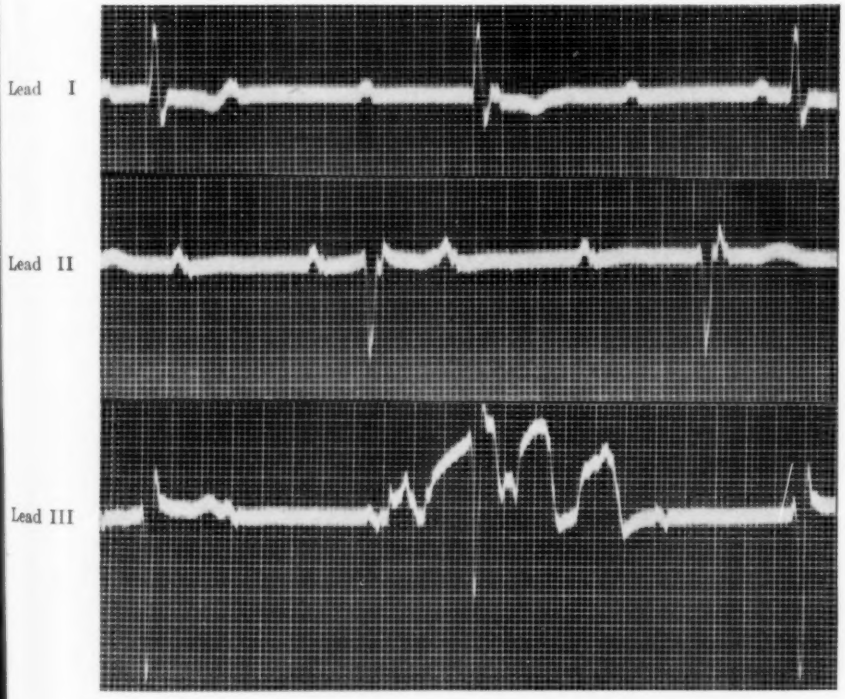


FIG. 2.—Same case. Electrocardiographic records taken one week prior to sudden death. Note short period of ventricular fibrillation in Lead III.

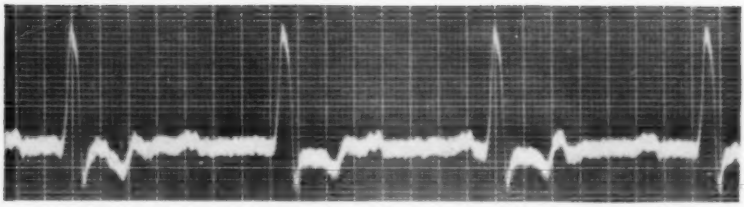


FIG. 3.—Lead I. Complete auricular and ventricular dissociation with right bundle-branch block. Note the rapid ventricular rate.

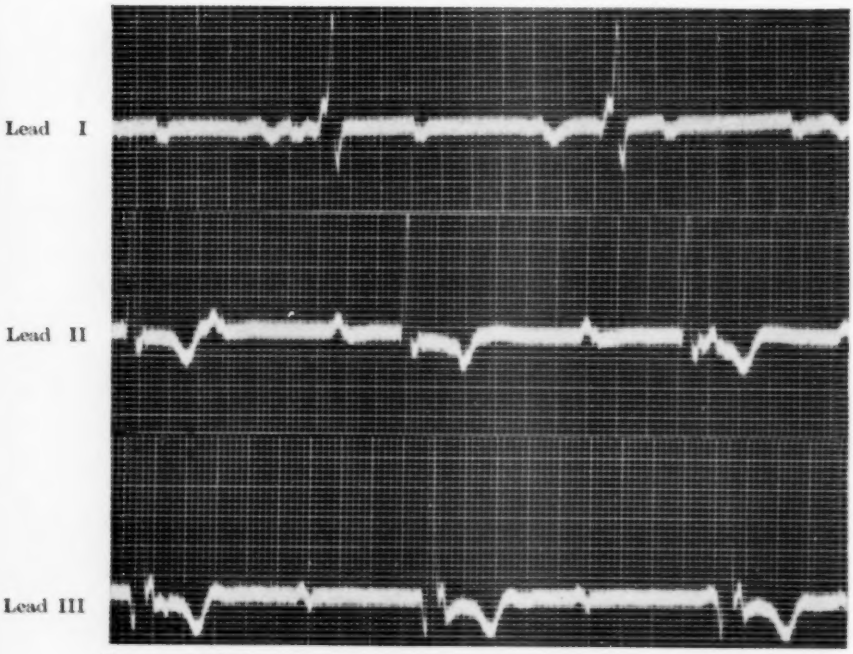


FIG. 4.—Auricular and ventricular dissociation with no axis deviation. Previous records showed a well-marked left axis deviation.

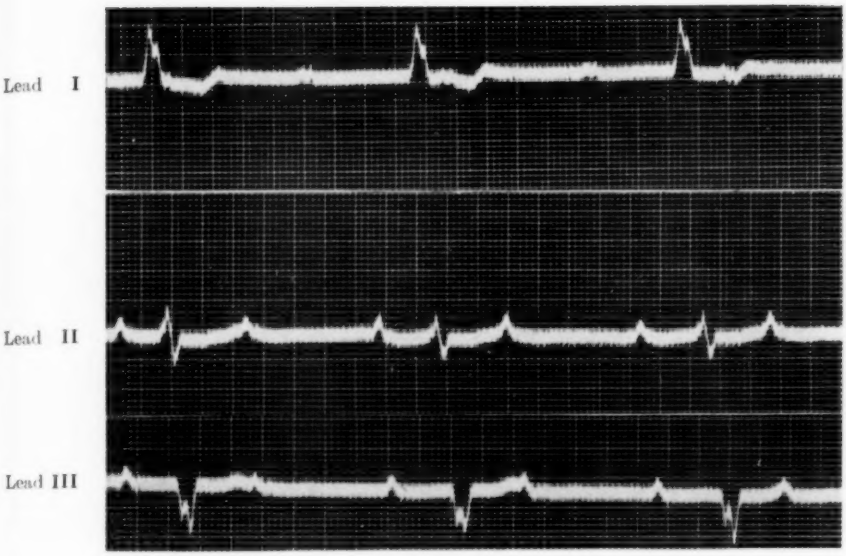


FIG. 5.—Complete heart block with right bundle-branch involvement.

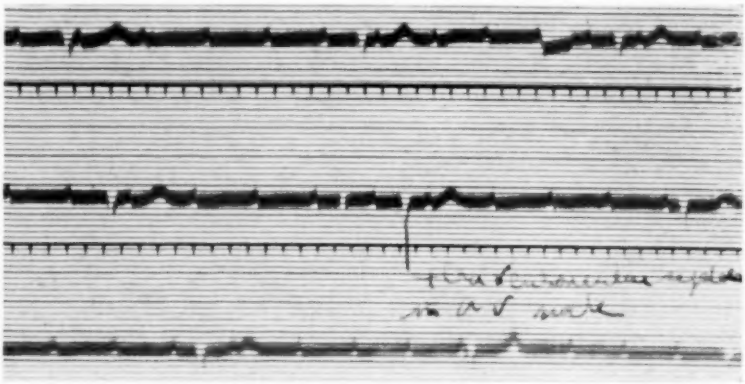


FIG. 6.—Electrocardiographic studies made in London by Sir James Mackenzie in 1922.

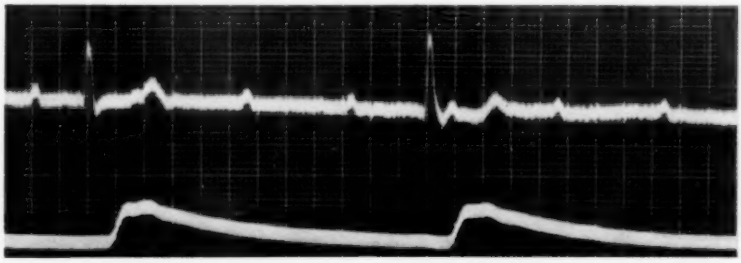


FIG. 7.—Simultaneous electrocardiographic and polygraphic studies made in 1928.

months, during which time no barium was given. On July 1 a final electrocardiogram was taken (Fig. 2), the ventricular rate was 28 beats per minute and the auricular rate was about 66. There were *T*-wave changes now only in the first lead, but there was a well-marked left axial deviation of the heart. During the taking of the third lead a short paroxysm of ventricular fibrillation was detected. One week later, on July 8, while on his way to our office, he dropped dead on the street.

CASE II.—B. D., female, aged sixty years, housewife, following climacteric changes of an unusually stormy type covering a period from the age of forty-seven to fifty-three years, during which time she maintained a persistently marked hypertension, was first seen by us at the age of fifty-seven years. At that time she was exhibiting fully all the after effects of prolonged hypertensive heart disease. Her dyspnea was especially distressing; electrocardiographic studies at this time revealed a marked left axial deviation of the heart with alteration of the *T*-waves in the first and second leads. There was a normal auriculoventricular rhythm. Routine therapy with prolonged bedrest was instituted. About fourteen months later, on March 10, 1927, the patient was seen again: the complaint at this time was the frequently occurring attacks of unconsciousness which developed even during sleep. Diagnosis of the Stokes-Adams syndrome was made upon the discovery of a complete auricular and ventricular dissociation; electrocardiographic studies were corroborative. The patient was immediately placed on six tablets of barium chlorid a day; on April 19, after having taken a total of 9.6 gm. of barium chlorid without any therapeutic improvement, the drug was discontinued. No difference either in frequency or duration of the attacks was observed. The patient is still alive; the attacks are perhaps less frequent than previously and no treatment except mild sedatives has been used for the past year.

CASE III.—W. D., male, aged fifty-nine years, street-car conductor, a man of unusual physique and giving a history of former athletic prowess, having been a hammer thrower, was suddenly stricken on the street with a dizzy spell. This attack was followed in subsequent weeks by similar seizures, some of these accompanied by lapses of consciousness. He came under our observation September 16, 1926, at which time a diagnosis of complete heart block with Stokes-Adams syndrome was readily made.

Electrocardiographic studies (Fig. 3) showed a right bundle-branch block, *T*-wave alterations in Lead I and a complete auriculoventricular dissociation. The auricular rate averaged about 80 and the ventricular rate was constant at 44. This case presents a rather unusual feature, namely, the Stokes-Adams syndrome in a relatively high ventricular rate. Barium therapy was instituted on October 3, 1926; four tablets were given daily until December 27, 1926, a total of 20.5 gm. was given. No appreciable result was noticed and therapy was discontinued.

After three years with little or no drug therapy the patient is still struggling along, dividing his time between chair and bed.

CASE IV.—P. S., male, aged sixty-six years, retired, came under observation on January 7, 1928, with a history of Stokes-Adams seizures for the past year. He had been studied in several clinics in this country and abroad. A large and varied collection of electrocardiographic tracings was presented to us: all were more or less similar and indicated a well established dissociation. This patient had experienced a remarkable array of therapeutic measures, scientific and otherwise, the only omission being that of barium. We considered this an excellent opportunity to demonstrate the efficacy of this remedy. Treatment was promptly started by

giving three tablets a day, which quantity was gradually raised until at the end of a month he was receiving eight tablets a day, which dosage was continued for another six weeks, making a total of 18.24 gm. of barium. To the chagrin of the family and ourselves, no change of any kind was noted and the drug was abandoned. The patient experienced no change in his condition but on December 10, 1928, while at dinner was seized with stenocardial pain and expired in a few minutes.

CASE V.—H. McG., male, aged fifty-one years, former bartender, with a long alcoholic history, negative Wassermann, was previously studied at a local cardiac clinic, where a diagnosis of complete heart block with the Stokes-Adams syndrome was made. The patient was referred to us for barium therapy. We began on May 26, 1929, with six tablets per day and continued on this dosage until August 4, a total of 18.24 gm. of barium having been administered. As in the previous cases, no change in the patient's status could be noticed. His condition at present is much aggravated by frequent attacks of coronary seizures in spite of the large doses of metaphyllin which he has been receiving.

CASE VI.—M. F., male, aged fifty-six years, jeweler, an obese individual weighing 248 pounds, with a long cardiovascular history has been under our care since March 8, 1927. At that time he showed rather typical electrocardiographic findings, a left axial deviation, *T*-wave alterations, and frequent left ventricular extrasystoles of the fundamental type. A régime of reduction by diet and mild physiotherapy was instituted with rather indifferent results, as the patient was decidedly noncoöperative. On June 12, 1928, following a burglar scare at his place of business he was found unconscious on the floor. It was thought that he had been attacked, but the attending physician, noting the extreme bradycardia, made a tentative diagnosis of heart block with the Stokes-Adams syndrome. After a period of hospitalization, during which time complete studies were made, a diagnosis of complete dissociation was confirmed. The electrocardiographic studies were interesting (Fig. 4) in showing not only the block phenomenon but the change in the electric axis of the heart. Where formerly there had been a well marked left axis deviation, now all of the *Q–R–S* complexes were upright. This observation is not an infrequent occurrence in complete block; many authors have noted the change from a left to a right deviation.

The patient left the hospital on a maintenance dose of twelve tablets of barium daily, the thought being that in an individual of such large proportions a greater dosage might be indicated. On August 2, after having taken 23.52 gm. of barium in forty-nine days, no improvement of any kind was noted. The patient continued to have rather frequent seizures of syncope, some of which were so severe that sphincter control was lost. With a basal metabolic rate of −35, thyroid was given with a double purpose in view: first, in an attempt to remedy the overweight factor and second, to determine its value in the Stokes-Adams syndrome. Some improvement was noted in both conditions for some time. The patient is still alive, refusing all treatment.

CASE VII.—H. G., aged sixty-eight years, merchant, male, has been known to us for the past seven years, during which time he has always had a bradycardia averaging about 30 to 40 beats per minute. Electrocardiographic studies made in 1923 showed a complete dissociation but the patient experienced no especial difficulties until 1928. He had retired from business and was leading a very regular but inactive life. On February 12, 1928, he suffered his first Stokes-Adams attack which lasted a few minutes; subsequent to this and occurring at more or less regular intervals he was seized

with attacks of syncope which were relieved without special therapy. On July 17, 1928, during a very hot spell, he experienced his worst attack and was unconscious for over an hour. He was given an intracardiac injection of adrenalin which seemed to have been somewhat effective. Of especial interest is the fact that there was no change in the ventricular rate during the period of unconsciousness, although the heart sounds were very much weaker. Barium therapy was instituted the following day and continued until November 10, 1928, a total of eighty-three days during which period 26.56 gm. were given. No therapeutic effect having been secured by this time, treatment with this agent was discontinued.

Electrocardiographic studies which were taken from time to time showed no or very little change (Fig. 5). This is a typical tracing; a right bundle-branch block was always present together with changes of the *T*-waves in Lead I. This patient is still alive and in the past two months bedridden.

Case VIII.—B. I. W., male, aged fifty-nine years, is extremely interesting in that he is a physician who has studied his own case over a period of about fifteen years. His description of the subjective symptoms for the entire course of his illness are picturesque and can only be related here but briefly. He was told in 1915 that he was suffering from "fatty heart" and high blood pressure: after a prolonged course of digitalis therapy he was forced in 1919 to give up the practice of medicine. In 1922, he was examined by Sir James Mackenzie, and electrocardiographic tracings taken in London (Fig. 6) showed a complete auricular and ventricular dissociation with a ventricular rate of 22 beats per minute. He came under our observation in 1927; he had no especial complaints and was living an extremely cloistered life. He had conducted a number of experiments upon himself and was well versed in cardiovascular literature. He had used no special remedies and was of the opinion that alcohol was of decided advantage in the treatment of heart block. On September 16, 1927, he experienced his first Stokes-Adams attack; it occurred while bending over to lace his shoes. He collapsed on the floor and was unconscious for about ten minutes. During the next two months he had eight such attacks and on November 20, at his request, he was placed on barium medication. At first he received only three tablets a day but this he increased to as high as fifteen. On January 1, 1928, after having taken 16.4 gm. of barium over a period of forty-one days with no change in the character or frequence of the seizures, we agreed to abandon it. He is back to his alcohol with apparent relief, the attacks now occurring about once a month and of shorter duration. He possesses a unique series of electrocardiographic tracings: Fig. 7 is a simultaneous electrocardiographic and polygraphic study.

His ventricular rate now averages about twenty-five beats per minute but at times he said that it has been as low as eighteen.

Summary. Table shows the specific details of barium therapy in 8 cases of auricular and ventricular dissociation exhibiting the Stokes-Adams syndrome. In no case did the barium exert any influence, either good or bad, upon the frequency or severity of the seizures, nor was the progress of the myocardial changes altered.

Barium chlorid was given in doses ranging from 0.16 to 0.4 gm. per day. It was administered in one case as long as one hundred and twenty-six days and in no case less than forty days. The total amount of barium taken altogether varied from 9.6 to 40.32 gm.

SUMMARY OF RESULTS.

Case No.	Sex.	Age.	Dose in 24 hours.	Days given.	Total barium.	Results.
1	M	56	0.320	126	40.32	Died.
2	F	60	0.240	40	9.60	Unimproved.
3	M	59	0.160	79	20.50	Unimproved.
4	M	66	0.320	62	18.24	Died.
5	M	51	0.240	69	18.24	Unimproved.
6	M	56	0.480	49	23.52	Unimproved.
7	M	68	0.320	83	26.56	Unimproved.
8	M	59	0.400	41	16.40	Unimproved.

The series comprised 7 males and 1 female, and the ages varied from fifty-one to sixty-eight years. There were 2 deaths in this series, but neither one of them occurred in a period less than three months after the administration of the barium.

The doses used in our series of cases are far larger and extended over a longer period of time than any previously reported cases. We have been unable to demonstrate any effect from barium chlorid when given by mouth and in doses far in excess of those suggested by authors who have obtained favorable results with this substance in the treatment of complete heart block with Stokes-Adams syndrome.

While this series of 8 cases is not large, Stokes-Adams syndrome is by no means common; we, therefore, feel that the series is extensive enough to challenge the test of barium efficacy.

REFERENCES.

1. Parsonnet, A. E., and Hyman, A. S.: Applied Electrocardiography, Macmillan, New York, 1929, p. 70.
2. Mackenzie, James: Diseases of the Heart, London, 3d ed., 1921, p. 274.
3. Harris, K. E.: Notes on a Case of Complete Heart Block of Unusually Long Duration, Heart, 1929, **14**, 289.
4. Willius, F. A.: Ann. Clin. Med., 1925, **3**, 129.
5. Russel, Wells and Wiltshire: Lancet, 1922, i, 984.
6. Lewis, Thomas: Clinical Disorders of the Heart Beat, London, 1918, p. 121.
7. Phear, A. G., and Parkinson, J.: Adrenalin in the Stokes-Adams Syndrome, Lancet, 1922, i, 933.
8. Danielopolu, D., and Danulescu, V. C.: Soc. de Biol., 1916, **79**, 861.
9. Cushny, A. R.: Pharmacology and Therapeutics, London, 9th ed., 1928, p. 387.
10. Routier, D.: Compt. rend. Soc. de biol., 1915, **78**, 375.
11. Herman, G. R., and Ashman, R.: Am. Heart J., 1926, **1**, 269.
12. Drake, E. H.: Am. Heart J., 1928, **3**, 560.
13. Blackford, J. M., and Willius, F. A.: AM. J. MED. SCI., 1917, **154**, 585.
14. Erlanger, J.: Arch. f. d. ges. Physiol., 1909, **127**, 77.
15. Rothberger, C. J., and Winterberg, H.: Arch. f. d. ges. Physiol., 1911, **142**, 461.
16. Wilson, F. N., and Herman, G. R.: Arch. Int. Med., 1923, **31**, 923.
17. Cohn, A. E., and Levine, S. A.: Arch. Int. Med., 1925, **36**, 1.
18. Levine, S. A.: Boston Med. and Surg. J., 1926, **195**, 1147.
19. Levine, S. A., and Matton, M.: Heart, 1926, **12**, 271.
20. Parsons-Smith, B. T.: Proc. Roy. Soc. Med., 1927, **20**, 23.
21. Strauss, S., and Meyer, J.: Am. Heart J., 1928, **3**, 328.
22. Price, F. W., and Nisse, B. S.: Am. Heart J., 1929, **5**, 197.
23. Heard, J. D.: Marshall, W. R., and Adams, F. S.: Am. Heart J., 1927, **2**, 562.
24. Puckner, W. A., and Leech, P. N.: J. Am. Med. Assn., 1929, **93**, 1627.
25. Leake, C. D.: J. Am. Med. Assn., 1929, **93**, 1632.

A STUDY OF UNINFECTED MURAL THROMBI OF THE HEART.

By Earle A. Harvey, M.D.,

and

Samuel A. Levine, M.D.,

senior associate in medicine, peter bent brigham hospital, boston.

(From the Medical Clinic of the Peter Bent Brigham Hospital, Boston.)

A cardiac mural thrombus is an antemortem blood coagulum formed on the inner surface of the heart. It is characterized by being adherent to the endocardium, gray or grayish-red in color, granular, friable and microscopically may show definite organization. It is easily separated from the postmortem or agonal clots, since these usually are nonadherent and are pale, yellowish, smooth, elastic, gelatinous masses which do not show evidence of organization. The present study was limited to uninfected thrombi. Criteria of infection were based on general appearance, cultural and microscopic examination of stained sections and the clinical entity involved.

These thrombus masses in the early days were called polyps because of their similar appearance to nasal polyps. Many of the earliest observations are now of doubtful value since no clear-cut distinction was made between agonal clots, various tumor masses and true thrombi occurring on the endocardial surface of the heart.

In 1809 Allan Burns[1] clearly described polyps or thrombi of the heart and supported the validity of the existence of such polyps. He noted the presence of such a polyp in the heart of a sufferer of angina pectoris. In 1814 William Wood[2] made the first observation of a loose thrombus (ball thrombus) in the left auricle in a case of mitral stenosis. In 1872 Zahn[3] produced a thrombus mass by injury to vessel walls and by placing a foreign body into the circulation. Later, Eberth and Schimmelbush[4] observed the early formation of a thrombus under the microscope in the living mesenteric vessel of a dog. As far as can be determined, thrombi have never been produced experimentally in the heart without first causing cardiac infarction. In 1909 Welch[5] wrote an extensive paper on thrombosis, including thrombi of the heart. He discussed the structure, formation and etiology of thrombi.

A study was made of all the necropsy protocols at the Peter Bent Brigham Hospital for the interval 1913 to 1929 in which 2091 records were reviewed. The incidence of thrombi of the heart in patients coming to necropsy was found to be approximately 5.3 per cent, or 111 instances in 2091 necropsies. The general distribution during these sixteen years was fairly constant with a tendency for the

proportion to increase latterly because of the larger number of patients admitted who were suffering from extreme cardiovascular disease.

Considering the sex incidence of these cases, 73 occurred in males and 38 in females. Thus, the frequency appears to be about twice as great in males as in females. As will be seen below, this probably is caused by the greater frequency of coronary artery disease in the males. It is apparent from Table I that thrombi occurred with greatest frequency in the later years of life. The two decades from fifty to sixty-nine included more than half of all the cases.

TABLE I.

Decades.	No. cases.	Per cent.
10 to 19	1	1.8
20 to 29	1	
30 to 39	16	14.4
40 to 49	20	18.0
50 to 59	32	28.8
60 to 69	32	28.8
70 to 79	9	8.1

In 100 cases in which the Wassermann test was recorded, 89 per cent were negative, 10 per cent ++ and 1 per cent +. This is about the average incidence of a positive Wassermann in all cases coming to the hospital and, therefore, cannot be regarded as significant.

A study of Table II throws light on some interesting relations concerning the sites of thrombus formation. In this series the frequency of thrombi was slightly greater in the auricles than in the ventricles. The two most common sites of thrombus formation were the tip of the left ventricle and the right auricular appendix. This was true for both isolated and multiple thrombi. Thrombi were found to be slightly more frequent on the left side of the heart than on the right (87 to 72). In analyzing the condition in the auricles and the ventricles separately, however, there was a great predominance in the right auricle as compared to the left (60 to 28) and in the left ventricle as compared to the right (59 to 12).

TABLE II.

Location.	No. cases.
Left ventricle alone	31
Right ventricle alone	4
Left auricle alone	6
Right auricle alone	28
Right auricle and left ventricle	11
Right auricle and left auricle	11
Right ventricle and left ventricle	5
Left auricle and right ventricle	2
Left auricle and left ventricle	2
Right auricle, left auricle and left ventricle	5
Right auricle, left ventricle and right ventricle	4
Right auricle, left auricle and right ventricle	1
Left auricle, left ventricle and right ventricle	1

It is apparent from a study of the pathologic finding in these cases that the sequence of coronary artery disease, cardiac infarction and mural thrombosis of the ventricles is the most common mechanism of the production of thrombi in the chambers of the heart.

The weights of the hearts were recorded in 103 cases and are indicated in Table III. From the table it will be seen that in about 92 per cent of the hearts the weights were considerably greater than normal, that is, over 400 gm.

TABLE III.

Weight of heart, gm.	No. cases.	Per cent.
200 to 300	3	2.9
300 to 400	6	5.8
400 to 500	19	18.4
500 to 600	36	35.0
600 to 700	24	23.3
700 to 800	8	7.8
800 to 900	6	5.8
900 to 1000	1	0.9

There were several types of anatomic conditions of the heart associated with thrombus formation. The majority had more or less generalized vascular disease of one form or another with myocardial degeneration; the next large group had valvular disease; there were 8 instances of syphilitic aortitis and 5 cases of rheumatic pericarditis. Of the valvular cases all 18 had mitral stenosis, 5 had aortic stenosis as well, 3 had tricuspid stenosis and 2 had, in addition, both aortic and tricuspid stenosis.

TABLE IV.

Location of infarct.	Incidence.
Pulmonary infarcts	47
Renal infarcts	18
Splenic infarcts	12
Cerebral infarcts*	3
Thrombosis of peripheral vessels.	**Incidence.**
Femoral artery	2
Left internal iliac artery	1
Superior mesenteric artery	2
Middle cerebral artery	1

* Because in some instances the autopsy did not include the examination of the brain, this figure is probably lower than is actually the case.

The incidence of secondary peripheral emboli and infarction from these thrombi was studied and the results shown in Table IV. The data recorded are explainable on the basis of embolism arising from thrombi located in the proper side of the heart. Cases were not recorded where thrombi occurred in the right side of the heart and infarction took place in the peripheral vessels or organs other than the lungs. It is not possible to conclude that all the recorded infarctions were caused by emboli from crumbling, friable thrombi,

since in some instances the etiology may have been extensive local atheroma of the vessel walls. In the pulmonary group the infarctions of the lung may well have been caused by local changes in the pulmonary vessels, resulting in stasis and infarction. The relative percentage of each mechanism of thrombosis and infarction is difficult to decide.

Of the 34 cases of single auricular thrombi, 19 had embolic phenomena, or 56 per cent. Of the 35 cases of single ventricular thrombi, 15 showed emboli, or 43 per cent. In other words, auricular thrombi were slightly more apt to produce peripheral emboli. Of 32 cases of single thrombi on the right side of the heart, 19 had embolic phenomena, or 59 per cent. Of the 37 cases of single thrombi on the left side of the heart, 15 showed emboli, or 40 per cent. It seems that no matter where the thrombus may be, whether ventricle or auricle, left or right side, the likelihood of resulting emboli is about 33 to 50 per cent.

The general complaints that these patients presented were those commonly associated with cardiovascular-renal problems. Physical examination of the heart showed the usual findings that occur in valvular or myocardial disease. In 85 of the 111 cases there was a definite increase in precordial dullness as determined by percussion. Auscultation revealed murmurs in general accord with the valvular lesions. In 32 cases no murmurs of any character were noted. Poor quality of the heart sounds were recorded in 13 instances, gallop rhythm was present in 11 cases, and systolic murmurs at the apex occurred in 64. An electrocardiographic study was made in 87 cases of this series. Of the irregularities found, heart block of various degrees formed the largest group (32), auricular fibrillation was present in 30 instances and premature ventricular beats occurred in 20 cases. Paroxysmal tachycardia was rare. Sixteen cases showed an abnormal form of the ventricular complex in the electrocardiograms. A study of the kidney function in some showed the usual findings associated with severe cardiovascular-renal disease. Blood pressure studies were unsatisfactory, since many of the patients were under observation a relatively short period of time. Approximately 50 per cent had an elevated blood pressure.

Special Groups of Selected Cases. (*a*) *Cardiac Infarction with Thrombi.* There were 37 with cardiac infarction in the entire group; of these, 27 were males and 10 were females. Thus in this group males were nearly three times as frequent as females, while in the unselected group males were not quite twice as frequent as females. The average age for females was 62.3 years, for males 59.5 years and the combined average was 60.3 years. There was only 1 case of valvular disease and that showed healed endocarditis of the aortic valve. The coronary arteries were all diseased except three which were recorded as normal. This group included the 22 cases of complete occlusion of the coronary arteries. The site of single

thrombus formation was 22 in the left ventricle, 1 in the right ventricle and 1 in the right auricle. The location of multiple thrombosis was 4 in the left and right ventricles; 6 in the right auricle and left ventricle; 2 in the right auricle, left ventricle and right ventricle; 1 in the right and left auricle and left ventricle. It will be seen from these data that in coronary thrombosis and cardiac infarction thrombi form chiefly in the ventricles and predominately on the left side of the heart. In this series there were only 9 instances of right auricular and 1 case of left and right auricular thrombosis. Ventricular thrombi were present in all the cases.

(*b*) *Chronic Valvular Disease.* There were 18 cases in this group. Eleven were females and 7 males. The average age of the females was 45.9 years, and for the males 38.1 years. The average age for the entire group was 42.8 years. In this series, as in the preceding group, the females outlived the males. The males have a high incidence of coronary artery disease and a low incidence of valvular disease while the females have a greater frequency of valvular disease and a low rate of coronary artery disease.

In the unselected group thrombi were almost five times as frequent in the right auricle as in the left. In the group (8 cases) of uncomplicated mitral stenosis thrombi were found four times in the left auricle, twice in the right auricle and twice in both the right and left auricle. Thus it would appear that mitral stenosis increased the frequency of left auricular thrombosis. In the 5 cases of mitral and aortic stenosis thrombosis occurred 5 times in the right auricle, twice in the left auricle and once in the right ventricle. In 3 instances of mitral and tricuspid stenosis the thrombi occurred in the right auricle in all cases. In 2 cases of mitral, aortic and tricuspid stenosis thrombus formation occurred once in each auricle. Considering the 18 cases as a whole, there is some slight evidence that valvular disease may effect the location of thrombi. This is especially true of pure mitral stenosis cases. In this entire series it is interesting to note that ventricular thrombosis occurred only once and that was on the right side.

A comparative study of the frequency of pulmonary and peripheral emboli was made for valvular cases and coronary artery cases having complete occlusion of one or more branches of the arteries. Of the 18 valvular cases 17 had associated pulmonary infarcts and only 6 peripheral infarcts. In the 22 cases of coronary artery disease with cardiac infarction and formation of thrombi, pulmonary infarction occurred in 5 instances while peripheral infarction occurred 13 times. Thus coronary artery disease with mural thrombi is associated with a higher frequency of peripheral embolic phenomena into the general circulation while valvular disease is more likely to be associated with pulmonary infarction.

(*c*) *Auricular Fibrillation with Thrombi.* In 31 cases there was good clinical evidence of persistent auricular fibrillation. This

group was selected in order to study the effect of this irregularity on the site of formation of cardiac mural thrombi. Thrombi were found in the right auricle in 10 instances and in the left auricle in 5 cases. There were 8 cases in which thrombi occurred in both the right and left auricles; 3 cases with thrombi in the right auricle, left auricle and left ventricle; 1 case with left auricular and right ventricular thrombosis; 1 case with right auricular, left auricular and right ventricular thrombosis. There were 3 cases with single thrombi in the left ventricle. Two of these were accounted for by the fact that they were instances in which auricular fibrillation developed after coronary thrombosis. The third case had an infarct probably caused by coronary disease, although the actual condition of the coronary arteries was not recorded in this instance. There were 5 other cases in which ventricular thrombi occurred together with auricular thrombi. There was no gross disease of the coronary arteries sufficient to account for the ventricular thrombi. In this series thrombi occurred in the right auricle in 22 instances, 18 in the left auricle, 6 in the left ventricle and 2 in the right ventricle. Thrombi occurred in the auricles 40 times as against 8 times in the ventricles. Right auricular thrombi were more frequent than left auricular thrombi (22 to 18), while left ventricular were more common than right ventricular thrombi (6 to 2). Fifteen of the 31 cases in this series had chronic valvular endocarditis.

It follows from the above that of the 31 cases who had auricular fibrillation, all but 3 had auricular thrombi (90 per cent). Of the other 80 cases in this entire series that did not show auricular fibrillation only 43 had auricular thrombi (54 per cent). There can be no doubt but that auricular fibrillation increases the incidence of thrombus formation within the auricles.

(*d*) *Ball Thrombi.* In this series of cases there were 2 instances of ball thrombi. Both cases presented the usual finding reported by Goljajew[6] in that they occurred in the left auricle in cases of mitral stenosis.

(*e*) *Heterogeneous Group.* There were 39 cases which did not fall into any large well-defined group. Analysis did not reveal any significant facts.

Mechanisms of the Formation of Cardiac Mural Thrombi. (*a*) Coronary vascular disease with occlusion or thrombosis of the lumen generally results in myocardial infarction. Wearn[7] has shown that if the process of obliteration of the coronary arteries is slow the vessels of Thebesius gradually may become able to supply to some degree the needs of the heart muscle, and gross infarction may not occur or at least may be less extensive. When the infarcted myocardium involves the endocardium there is probably a liberation of tissue juices which enhances the formation of a mural thrombus. This mechanism accounts for one-third the total number of cardiac mural thrombi.

(*b*) A second method of formation seems to depend mainly on stagnation of blood in the auricles. Several factors probably play a part in bringing about the final result. Certainly such a functional irregularity as auricular fibrillation effects profoundly the normal flow of blood from the auricle to the ventricle. This combined incoördination of the auricles and the ventricles and the lack of an effective auricular contraction tend to cause stasis in the recesses of the auricle. Disease of the myocardium as caused by rheumatic fever and syphilitic infection may weaken the strength of contraction as evidenced by the replacement of muscle with fibrous tissue. Stenosis of the valves with associated regurgitation slows the flow of blood, increases the work of the heart and favors stagnation of blood in the auricles. Moreover, dilatation of the auricles so common in congestive heart failure adds to the other harmful factors in producing stagnation of blood and in impairing the health of the myocardium and especially of the underlying endocardium. The fact that over 75 per cent of auricular thrombi in this series occurred in the auricular appendices emphasizes the importance of stagnation of blood as a factor in the formation of mural thrombi.

Diagnosis of Cardiac Mural Thrombi. The antemortem diagnosis of cardiac mural thrombosis offers many difficulties. There has never been reported any sign or group of signs that are pathognomonic. Although the finding of cardiac thrombi is not uncommon at necropsy, it is still a rare clinical diagnosis. This is accounted for by the fact that they so frequently remain silent throughout the course of the disease and then form only an incidental postmortem finding. There are certain cases when a thrombus may be suspected. Cases of coronary thrombosis with evidence of peripheral embolism will be found to have a high incidence of cardiac mural thrombosis. Chronic valvular heart disease with auricular fibrillation and evidence of either pulmonary or peripheral infarction will almost surely have cardiac thrombi. Necropsy shows that approximately 20 per cent of hearts with chronic valvular disease and 84 per cent with coronary thrombosis have cardiac mural thrombi. Consideration must be given to the type of case, age limits and presence of other constitutional disease. There will be left a large group in which the thrombi remain silent and give no evidence of their presence and are only to be found at necropsy.

Summary. 1. Uninfected antemortem mural thrombi of the heart were found in 5.3 per cent of all necropsies performed at the Peter Bent Brigham Hospital.

2. Cardiac mural thrombi were twice as frequent in males as in females. The majority of these patients died between the ages of forty to seventy years. The cases with ventricular thrombi following cardiac infarction formed the oldest age group (sixty-two years). There was a large middle-aged group with valvular disease (forty-five years).

3. The frequency of sites of formation of single mural thrombi were: left ventricle, 31; right auricle, 28; left auricle, 6; right ventricle, 4. There were 42 cases of multiple thrombosis. The apices of the ventricles and the auricular appendages were the most frequent sites of formation for mural thrombi.

4. Secondary infarction outside the heart as a result of emboli occurred with the following frequency: pulmonary, 47; renal, 18; splenic, 12; cerebral, 3 (the brain was examined in only a limited number of instances). There were 6 instances of peripheral arterial thrombosis that may have been embolic.

5. Auricular fibrillation definitely increases the incidence of auricular thrombosis.

6. The two most frequent mechanisms for the formation of cardiac mural thrombi are the myocardial degeneration associated with coronary arterial disease and the improper functioning of the auricles leading to blood stasis.

7. The diagnosis of cardiac mural thrombosis presents difficulties, but should be suspected in cases of coronary thrombosis and chronic valvular disease showing evidence of emboli.

NOTE.—We wish to acknowledge the aid rendered by the pathologic department of the Peter Bent Brigham Hospital in furnishing the data.

REFERENCES.

1. Burns, Allan: Observations on Formation of Polypi of the Heart, Diseases of the Heart, 1809.
2. Wood, William: Communication to Edinburgh Med. and Surg. J., 1814, **10**, 50.
3. Zahn: Untersuchungen über Thrombose, Virchow's Arch., 1875, **62**, 81.
4. Eberth and Schimmelbush: Die Thrombose nach Versuchen u. Leichenbefunden, Stuttgart, 1888.
5. Welch, W. H.: Thrombosis, Albutt's System of Medicine, 1909, pp. 691–821.
6. Goljajew, A. W.: Ball Thrombi of the Heart, Frankfurter Ztschr. f. Pathol., Munich, 1927, **35**, 409.
7. Wearn, J. T.: The Rôle of the Thebesian Vessels in the Circulation of the Heart, J. Exp. Med., 1928, **47**, 293.

FLARIMETER TESTS OF CIRCULATORY FITNESS.

A PRELIMINARY REPORT.

BY L. F. MACKENZIE, M.D., P. V. WELLS, D.SC.,
E. G. DEWIS, M.D., AND L. S. YLVISAKER, M.D.,
NEWARK, N. J.

(From the Medical Department of The Prudential Life Insurance Company of America.)

ABOUT two and a half years ago, stimulated by the painstaking work of H. M. Frost,[1] of the New England Mutual Life Insurance Company, and feeling the urge for some test which seemed to us

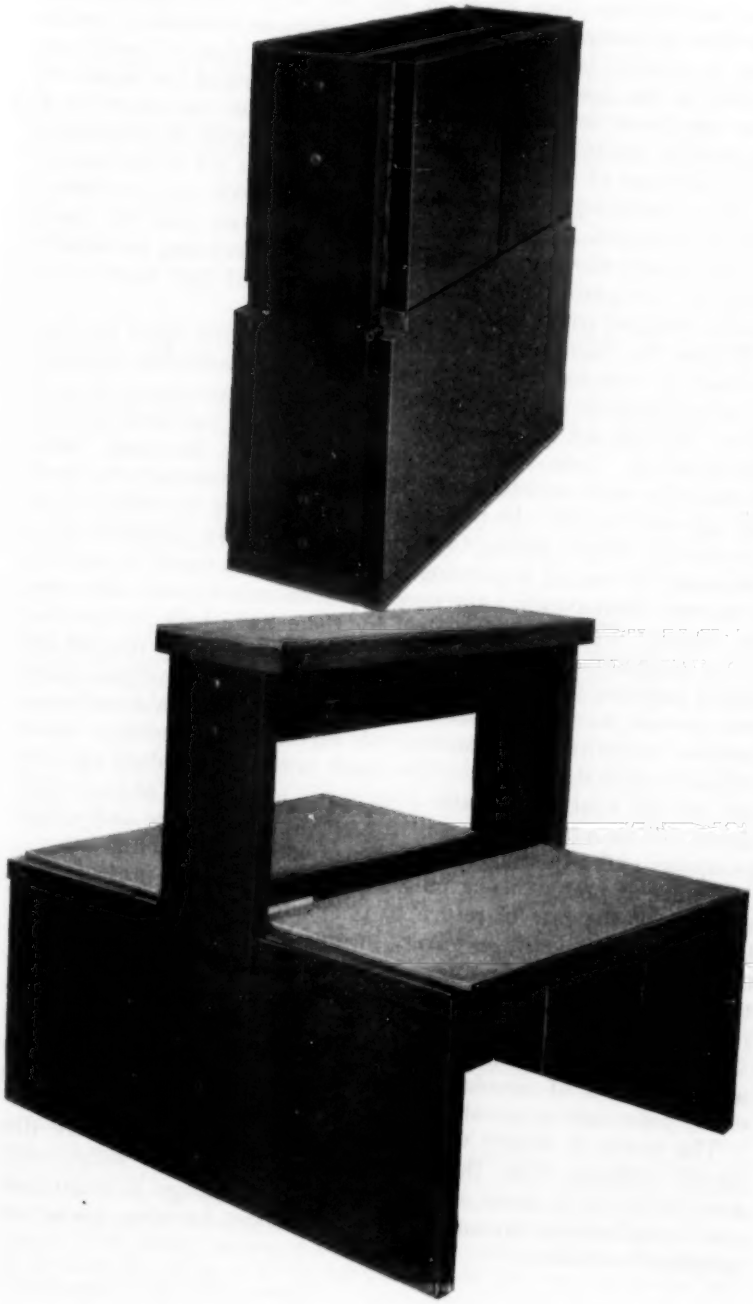


FIG. 1

more satisfactory than those in use, we began investigating our reactions to changes in intrathoracic pressure as revealed by variations in systolic, later in diastolic pressure, and then in heart rate counted at the apex. Our experiences and review of the literature soon convinced us that accurate standardization was essential if comparable results were to be obtained. We wish to emphasize the importance of this, as doubtless lack of it has led to statements by many cardiologists that these tests are of little value in determining myocardial efficiency. We are convinced that the fault was more with the method than the tests. There being no reliable basis for comparison, as no constant standard had been used, results obtained could scarcely be satisfactory.

Within the past year Master and Oppenheimer[2] have brought forward an exercise test which has made standardization possible, for when carefully applied it permits accurate measurement of work done. It will not be described here because it has been so ably presented by them. They provided tentative standard tables showing the work which should be performed by normals of a given sex, age and weight; the pulse and blood pressure to return to the pre-exercise figures within two minutes. We have simplified these tables for our use by expressing the work done in terms of numbers of ascents, thus avoiding the necessity of calculation and correction for height. The steps described by them have been so modified by us that they are now portable and may be quickly opened and folded together (Fig. 1). A simple, convenient and well-standardized exercise, to which all are accustomed, is now available and comparable quantitative measures of myocardial condition under ordinary methods of examination made possible. As data accumulate and are analyzed, greater accuracy in application and interpretation will be attained by splitting up the present age and weight groupings and adjusting the number of ascents for each group.

We are at present using pulse rather than systolic pressure as a measure of the rate of return to pre-exercise values. Records of both are being kept, however, in the hope that later, through comparison, their relative merits may be established. The importance of shortening of breath developed by this exercise and accurately measured by the flarimeter will be explained later. This shortening, moreover, with rate of its return, gives promise of being a better index of circulatory response to standard exercise than either pulse rate or systolic pressure.

The series of events which occur during the exercise are distinctly different from those which take place when instruments are used to throw strain on the heart through changes in respiration and intrathoracic pressure. The differences between them are tabulated as follows:

Exercise Test.	*Respiratory Test.*
1. Little change in intrathoracic pressure.	Pronounced change continuing throughout the blow.
2. Increased respiration with gradual return to normal.	Increase in respiration only after the test and quick return.
3. No interruption in flow of blood into the right auricle.	Marked but temporary interruption of venous return.
4. No diminution in pulmonary circulation.	Marked but temporary diminution.
5. Lactic acid accumulation with oxygen debt.	Slight, if any.
6. Fatigue.	Fatigue, except of lips, absent.
7. Return of pulse rate to normal delayed in proportion to oxygen debt.	Return of pulse rate to normal more rapid.

Respiratory tests will be described under two headings: (1) Vital capacity and (2) breath holding.

Description of Flarimeter. Before discussing these, however, a simple instrument which we designed and which made possible the use of a definitely known intrapulmonary pressure will be described. The instrument developed to its present form, and named the Flarimeter (from "Flare," to blow), is pictured on the next page (Fig. 2). It has enabled us to make observations on the relative values of and comparisons between vital capacity, breath-holding ability, systolic and diastolic blood pressure, heart rate and stroke volume. Briefly described it consists of a glass bottle partly filled with water; the remaining space furnishing an air chamber. The bottle is closed by a tightly fitting rubber stopper having three perforations and capped with a metal plate which serves as a base for three stopcocks and two orifices. Three metal tubes pass downward from the plate through the stopper. One, marked to indicate the required height of water in the bottle, extends to within 2 mm. of the bottom. Its other end, above the plate, is so formed that it contains a stopcock, *B*, over which is a socket, serving when the instrument is in use, to hold a detachable glass manometer tube *A*. This tube is guarded by a valve at the top, to prevent jets of water being blown out, and is in direct connection with the water when the stopcock is open. The second and third tubes pass through the stopper into the air chamber and are also so formed above the plate that each is opened and closed by a stopcock. To one (*C*) is attached a rubber tube of specified length and caliber, at the other end of which is a metal mouthpiece *E*. Through this air is blown into the chamber, forcing the water up the manometer tube to a point distinctly marked at 272 mm. H_2O (20 mm. Hg.) above the level of the water in the bottle. The third tube is so formed above the plate that, by means of a three-way stopcock (*D*) it brings either of two most carefully calibrated orifices into communication with the air chamber. The larger *L* of these permits a flow of 200 cc. of air per second, the smaller *S* of 36 cc. per second at a pressure of 20 mm. Hg. The arm of this stopcock turned to the right connects the large orifice, and to the left the small orifice, with the air chamber. When using the instrument the arms of the three stopcocks must be horizontal and are of such length that the box will not shut while they are in this position. When vertical the three openings into the bottle are tightly closed so that water cannot escape. The orifices are turned downward into the box to prevent any drops of water in the valves from being blown on to the instrument when the blow is begun. The entire instrument is fitted into a walnut-finished wooden case $8\frac{1}{2}$ by 4 by $2\frac{3}{4}$ inches, in which space is provided for the manometer tube, mouthpiece, and rubber tubing.

A very convenient and easily portable instrument capable of accurately measuring vital capacity with the large and breath-holding time with the small orifice is thus provided. It is durable with the exception of the rubber tubing which may be easily replaced. A more complete description is being published in the *Review of Scientific Instruments*.[3]

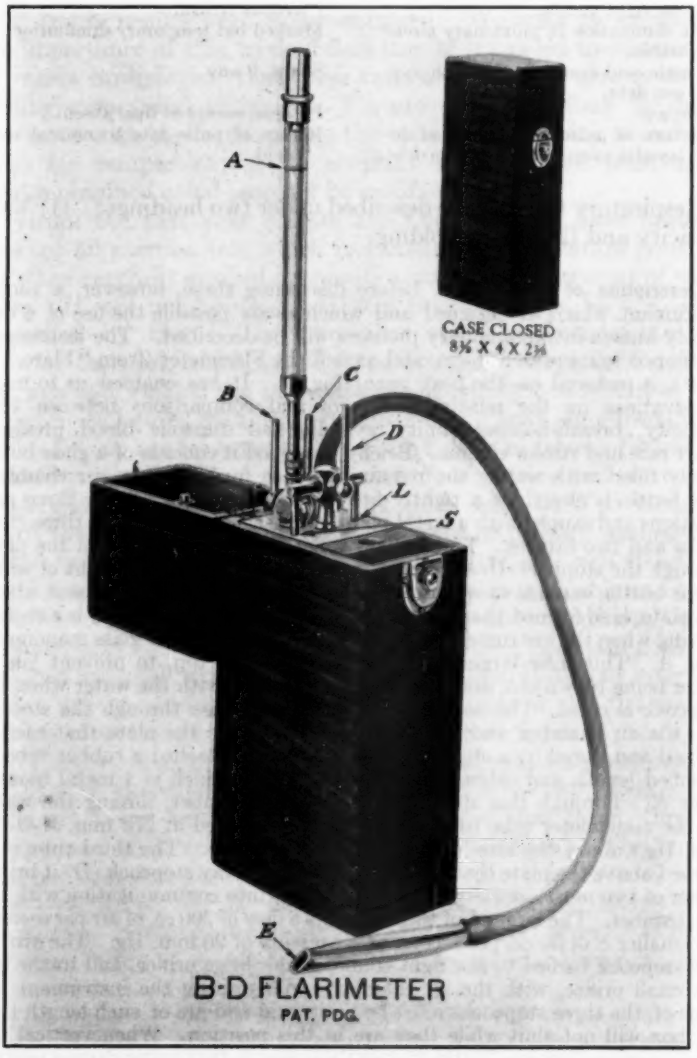


FIG 2

In measuring the vital capacity by the maximum length of blow through the large orifice, the two chief errors are personal to the subject; first, failure to maintain the pressure at the index level throughout the blow;

second, failure to fill the lungs completely before beginning the blow. These errors usually will exceed all the instrumental errors combined. If the examiner is careful, the length of blow can be estimated easily to half a second, which is only 2.5 per cent of a twenty-second blow.

It must be remembered that the pressure drop between mouthpiece and gauge is over 5 mm. Hg. when using the large orifice, so that the length and internal diameter of the rubber tubing are not to be changed. A new piece of the standard tubing should be ordered from the manufacturer* when the rubber deteriorates. With the small orifice, the flow is so small that the intrapulmonary pressure is actually that measured on the gauge.

A water manometer was chosen because it is more sensitive than a mercury and its fluctuations much larger (13.6 times). The psychic effect produced by the larger fluctuations tends to greater accuracy in maintaining the correct pressure. It is always more dependable than is an aneroid.

The accessories necessary are a reliable sphygmomanometer, preferably mercury, a stethoscope with a ribbon arm band to hold the diaphragm over the brachial artery just below the cuff and a watch with a second hand. To obtain sufficient responsé in systolic pressure, the rate of expiration must be controlled in order to get a cumulative effect. It is only in the later stages of the sustained expiration that the systolic and diastolic pressures rise considerably in normal subjects. If expiration is too rapid or too slow the response is not as pronounced as it is at the optimum rate, which we have found to be about 36 cc. per second when the intrapulmonary pressure is 20 mm. of mercury. This pressure has proved to be the most satisfactory. Heretofore such tests have been made either through large orifices, at many times the optimum rate, or when holding the breath, which is at zero rate of flow. The maximum responses obtained with small orifices are shown by the average values for twenty normal adult males.

TABLE I.—EFFECT OF SIZE OF ORIFICE.

Rate of flow (cc. per second) . .	0	24	36	48	72
Length of blow (seconds)	69	62	56	51	46
Volume expired (per cent of vital capacity)	0	37	51	62	84
Rise in systolic pressure (mm. Hg.)	16	24	27	25	13

The 36-cc. orifice was chosen because, as indicated by the above table, it produced the best systolic response with the least discomfort; the end of the blow being in the region of tidal breathing (51 per cent of the vital capacity). The individual tested can, therefore, blow more steadily and better control the duration of the physical effort, enabling the examiner to observe the systolic pressure at the end of the blow and the total length of blow with accuracy and ease. All a patient has to learn is to take a full inspiration and blow as long as possible, keeping the water level steady at the index mark. Less force is required to do this with the small orifice than with the large, but this change is learned quickly in a single practice trial.

Hutchinson,[4] in 1846, began his studies of vital capacity. Since that time it has had its ups and downs in popularity as an evidence of physical condition. In recent years it seems to be again coming into favor. MacLeod[5] writes: "It has become more and more evident since Peabody and Wentworth's researches, that a determination of vital capacity is of great importance in the diagnosis

* Becton, Dickinson & Co., Rutherford, N. J.

and prognosis of several diseases including heart disease and tuberculosis." Peabody[6] stated: "The vital capacity of the lungs in heart disease is an index of pulmonary circulation or interference of pulmonary movements on account of circulatory failure."

Whatever one's attitude regarding the possibility of specific interpretation of vital capacity, there can be little doubt that a subnormal value is presumptive evidence of physical impairment and that failure to reach the normal demands explanation. Securing full coöperation by patients is at times a real difficulty. However, the percentage of failures is very small when patience is exercised, combined with instruction and encouragement to do better.

Unanimity of opinion as to the value of this test is lacking among clinicians, many believing that physical examination will disclose an impairment which has progressed to the point where vital capacity has become subnormal and that it is such an individual characteristic that its comparison between persons is not of sufficient significance to make its use really valuable as a routine procedure in the examination of heart and lungs. This attitude will never solve the problem of its worth or convince those who are trying to obtain all possible evidence of physical condition, aids to prognosis and indications of progress under treatment. One fact seems well established, namely, changes in vital capacity in an individual show the progress of many heart and lung impairments.

The spirometers heretofore in use may have had something to do with this attitude, as they were not easily portable. We hope our instrument has overcome this difficulty and that use of the test in home or office is now an easy procedure.

Normally vital capacity is limited by the size of the thorax and flexibility of its walls so that the average values correlate closely with height, weight and surface area. The standard tables by height given by Myers seem to us more practical for general use than is surface area, though the latter gives a slightly closer correlation.

The borderline between normal and subnormal is stated to be 85 per cent by age and height. It is relatively larger in tall persons and in those under the age of forty years. After this age there is a gradual decline, which seems to be less than 1 per cent per year, although the literature indicates the fall is about 1 per cent. We have found that under normal conditions there is no correlation between it and breath-holding ability. The same observation has been made by Jackson and Lees,[8] who reported a correlation of but 0.16 ± 0.07 in 100 healthy male students. Wittich and Polczak,[9] on the other hand, found that vital capacity and breath-holding time ran parallel in tuberculosis and cardiorenal disease. Our preliminary studies have led us to the same conclusion, as scatter diagrams have shown the correlation increased with increase in severity of impairments.

Study of the literature, observations in this office and reports

from selected examiners have satisfied us that vital capacity is important, but confirmation of our views will have to await accumulation of data and lapse of time sufficient to give mortality ratios so conclusive that positive statements would be warranted.

Some investigators have believed the vital capacity to be a measure of shortness of breath because it is reduced in many cardiac affections. But a very simple experiment will convince anyone that the length of the flarimeter small orifice blow is a much better measure of shortness of breath than is vital capacity. Immediately after the standard step exercise the small orifice blow is shortened to less than a half of its normal length, while the vital capacity as measured on the Collins is not reduced at all. No change has occurred in the lung capacity. It is the "oxygen debt" in the blood and tissues which has shortened the small orifice blow. Of course, the flarimeter large orifice blow, which ordinarily measures vital capacity, is also reduced in length somewhat under such conditions because the breath-holding time is then a limiting factor.

Turning now to blows with the small orifice, which are really tests of breath-holding ability, we find they give evidence of oxygen depletion, carbon dioxid accumulation and ability of the heart to maintain necessary bloodflow under the strain imposed as a result of the changes in its composition and the increased intrathoracic pressure.

Valsalva's experiment seems to have been the first attempt to determine the effect on pulse rate of increased intrathoracic pressure. Sabrazés,[11] in 1902, found breath-holding time following quiet expiration to be about twenty to twenty-five seconds. Stange,[12] in 1914, gave it as forty-five to fifty seconds after maximum inspiration, and found it greatly reduced in pulmonary and cardiac disease. Henderson,[13] in the same year, pointed out that it was an index of acidosis, and that assuming the sensitiveness of the respiratory center constant the blood stimulus can be ascribed to two factors: (1) CO_2 and (2) other acids (or deficiency in alkali). Whenever the alkaline reserve is low the sensitiveness to CO_2 must be increased, and this we think is his explanation of the shortness of breath. Palcso,[14] in 1928, announced definite shortening in cardiac patients following exercise with marked correlation between this shortening and mortality.

Obviously voluntary apneic pause is a quantitative measure of shortness of breath and can be standardized to replace the qualitative descriptions of the past. The British Royal Air Force have taken as the standard an intrapulmonary pressure of 40 mm. Hg. and require a blow of not less than forty seconds. Bürger,[15] using intrapulmonary pressure of 40 to 50 mm. Hg. with a blow of twenty seconds, produced marked fall in arterial pressure with evidence of partial, or complete, collapse and considered that the blood-pressure reaction shown was an index of myocardial incompetence, as asthenic

hearts were unable to restore the systolic blood pressure to its rest value for over forty seconds. This test seems too severe for general use and quite out of the question in life-insurance examinations, especially as in some of his cases electrocardiographic tracings showed that premature contractions and changes in conduction time had developed.

During the small orifice blow there is first a marked rise in intrathoracic pressure which compresses the great veins and greatly reduces or completely shuts off the blood supply to the right heart. Arterial pressure, therefore, is materially lowered following a brief and sudden rise. These changes are mechanical, and if continued would very soon lead to circulatory standstill with collapse. This does not occur, however, unless the pressure applied is excessive or the individual too weak. Nothing approaching this condition has been observed in our work.

Meanwhile the venous pressure in the cistern of Keith has been mounting and soon exceeds that in the thorax. This is due to increased intraäbdominal pressure and vasomotor constriction of the splanchnic vessels squeezing the venous blood into the right heart, and so causing the arterial pressure to rise promptly from its low value. Venous pressure continues increasing to overcome a slowly increasing intrathoracic pressure as air leaves the lungs.

With the initial drop in arterial pressure, coronary and brain circulation are reduced, vasoconstriction of the systemic arterioles intervenes and diastolic pressure rises. Soon interference with aëration depletes the oxygen in the blood and CO_2 accumulates, requiring a steadily increasing bloodflow to compensate for its progressive deterioration. Heart rate, stroke volume, or both, increase, systolic and diastolic pressures mount rapidly and a vicious circle occurs which, if prolonged, leads to severe myocardial fatigue.

To protect the heart, something must stop the blow. The functional ability of the cortical centers (will power) is here largely a matter of oxygen supply. Increased expenditure of energy, in an effort to prolong the blow, combined with oxygen shortage, produce fatigue of these centers with loss of inhibitory control of the basal nuclei. On the other hand, emotional stimuli in nervous individuals may be so great that exaggerated reactions and shortened blows result. This latter is well illustrated in a paper by White,[16] giving results from tests made on soldiers during the World War. The price of apnea produced by this test is a rapidly increasing burden on the myocardium which can be relieved only by loss of voluntary control of the respiratory center.

It is obvious, therefore, that the nervous responses to the flarimeter test are largely characteristic of changes ordinarily taking place in the circulatory system and so intimately involve the heart. If such a load can be thrown on a normal heart, what must be the effect on a myocardium already impaired? Fraser[17] considers that

"the fundamental cause of cardiac dyspnea is inefficiency of the myocardium." If this is admitted, the length of the small orifice blow is a direct measure of myocardial efficiency, when due regard is given to the other factors which may influence shortness of breath in a given case. A diagram of the systolic reaction during a blow is shown in Fig. 3.

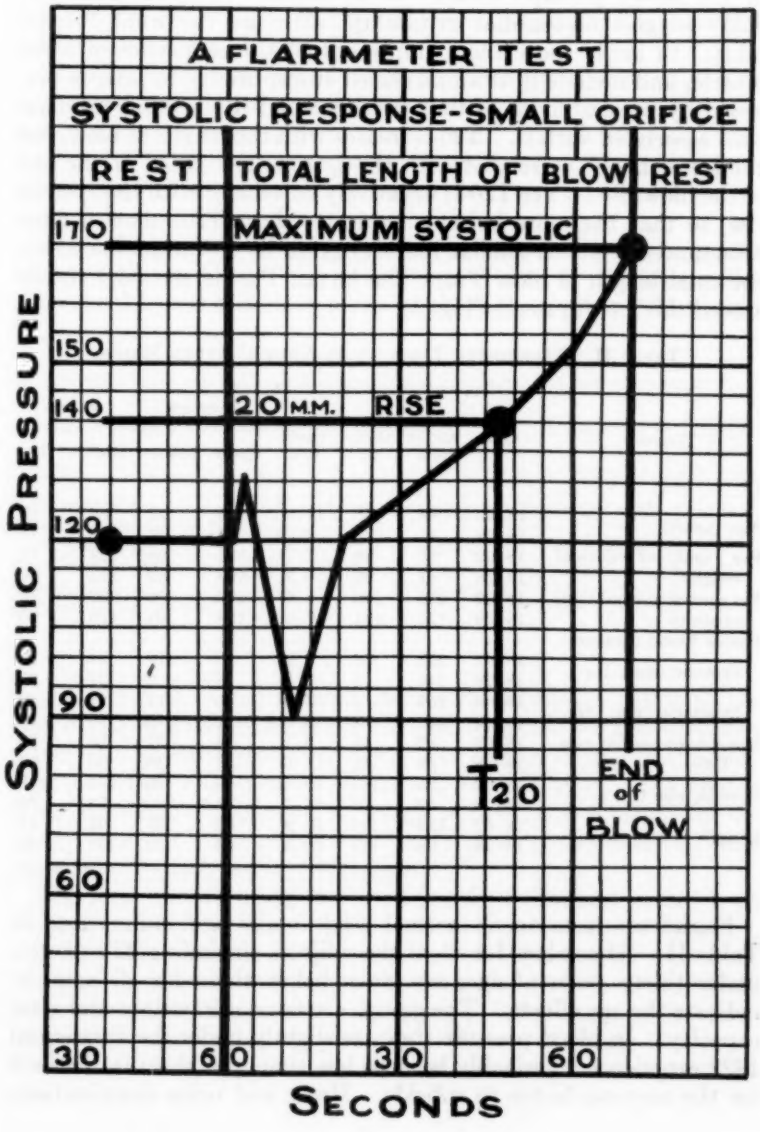


FIG. 3

It will be seen that the responses to the small orifice test are so gradual that it is fairly easy to obtain complete time curves of blood pressure and heart rate during an individual blow. In fact, all the tests in the home office are thus observed, to make sure that nothing is overlooked. So far T20 (the time required for the systolic to rise 20 mm.) seems more significant than the rise taken at the end of the blow, perhaps because it is better standardized. Short T20's suggest myocardial irritability. We use the word "irritability" to imply more than simply one of the properties of heart muscle, and include in it an increased susceptibility to fatigue preceded by hyperactivity of that structure and the nervous mechanisms associated with it. T20 increases with the length of blow, but the latter is not correlated with the systolic rise noted at the end of the blow S+. Yet T20 is negatively correlated with the systolic rise, so that the more irritable subjects (short T20) show a more pronounced S+. A similar index is given by S+ when it exceeds the total length of blow Tm. The latter, Tm (in seconds) should exceed the S+ (in mm.) (Fig. 3).

TABLE II.—FLARIMETER TESTS ON 88 NORMAL ADULT MALES.

Variable.	Ages.	No. of tests.	Median.	Deviation.	Quartiles. Upper.	Quartiles. Lower.	Range. High.	Range. Low.
Age (years)	18–62	88	30	11.0	43	22	62	18
	18–28	41	22	2.22	24	21	28	18
Per cent of normal weight	18–62	88	99	7.7	104	90	123	73
	18–28	41	98	6.3	103	89	113	80
Per cent of normal vital capacity	18–62	246	100	8.8	106	90	122	76
	18–28	120	101	7.3	108	94	119	80
Excess blood pressure:								
Systolic (mm. Hg.)	18–62	528	−4	9.3	6	−10	24	−30
	18–28	246	1	9.2	8	− 8	22	−22
Diastolic (mm. Hg.)	18–62	264	−5	7.5	0	−12	17	−29
	18–28	123	−9	6.6	−1	−15	10	−29
Seconds to rise 20 mm. (T20)	18–62	82	45	9.1	54	37	83	20
	18–28	39	44	8.5	53	36	63	23
Systolic rise (S+)	18–62	85	40	11.4	49	30	74	10
	18–28	39	40	11.3	48	30	74	20
Length of blow (Tm)	18–62	199	54	10.8	62	43	91	21
	18–28	95	47	10.3	58	39	91	31

Flarimeter tests on 88 normal adult males are summarized in Table II. The values for 41 of the subjects (including 22 athletes, under thirty years of age, are given below those for all ages, to indicate the age effects. The groups are normal in weight and vital capacity. In blood pressure they are slightly under the Prudential 1922 experience,[18] probably because less time was given in the field for the nervous factor to subside. Heart and urine examinations

revealed no significant impairments. The smallest variability in the flarimeter responses is in vital capacity, which gives an average deviation of single subjects from the median of about 9 per cent. The corresponding variabilities of T20 and Tm (the length of blow) are 20 per cent, and of the final rise (S+) 28 per cent of the respective median responses.

The upper and lower quartiles indicate the limits within which one-half the cases fall, so that the odds are against a normal response falling outside these limits.

The flarimeter tests are now being applied by selected examiners in the field and clinical cases are being studied. Preliminary results indicate marked reductions in vital capacity, length of small orifice blow and T20 in the more advanced clinical cases. There is positive correlation between these three quantities in the rated and rejected cases, but none among the standard risks.

Tentative normal limits are set up in Table III. To show the severity of the limits, the proportion of the 88 normals called subnormal by each limit is given in the last column. Thus, since

TABLE III.—TENTATIVE LIMITS FOR INTERPRETATION.

Variable.	Symbol.	Subnormal.	Normal.	Normals excluded by limit.
Vital capacity . . .	V	Under 85 per cent	Over 90 per cent	2 per cent
Time for systolic to rise 20 mm.	T20	" 25 seconds	" 35 seconds	6 "
Final systolic rise . . .	S+	" 20 mm.	" 30 mm.	5 "
Length of blow . . .	Tm	" 40 seconds	" 45 seconds	5 "
Difference (Tm − S+) .	. . .	" 0	" 10	6 "

only 2 per cent of the normals have vital capacities below 85 per cent of the standard of Myers (by height, corrected for age by adding 1 per cent for each year over forty), the chance is only one in fifty that a normal will be called subnormal by this limit. The chance is one in twenty (5 per cent) for length of blow, and similarly for the other responses. These limits will serve until further data furnish a more reliable basis for interpretation.

The form we are using to record the data obtained is shown on Table IV. It will be seen that a time schedule is required in Tests 3, 4, and 5. This seems to us very important. The stated "maximum systolic" applies to the height to which the systolic pressure has risen when the blow ceases. Frequently following a momentary drop there is a further systolic rise. We are studying this in an attempt to determine its significance. It does not occur in all cases.

TABLE IV.—SYNOPSIS OF TECHNIQUE FOR FLARIMETER TESTS.

Test I

Pulse Rate
Systolic Pressure
Diastolic Pressure (4th point)

Test II Repeat twice

Vital Capacity

Seconds × 0.2 = Liters

Test III Repeat twice

Seconds
25–45 **Systolic** Pressure — Deflate—Record
55–60 **"Inspire!"**
60 **"Blow!"**
Inflate—**T20** in seconds
Maximum Systolic
Total Length of Blow — Deflate—Record

Test IV

30–45 **Pulse Rate** — Record
30–60 **Systolic** and **Diastolic** Record — Remove cuff

Test V

Seconds
30–45 **Pulse Rate** — Record
20–60 } Standard exercise for 90 seconds
60–50 } See table for number of ascents
Record number of ascents

(If no steps are available, use 30 bending movements in 1 minute)

55–60 **"Inspire!"**
60 **"Blow!"**
Record length of blow
45–60 **Pulse Rate** (per min.)—Record
45–60 **Pulse Rate** (per min.)—Record

RECORD OF TESTS

Name .....Age.....Sex...?....Occupation.....Ht.....ft.....ins. Wt.....

I.		II.		III.				IV.		V.	
At rest		Vital capacity Sec.	Liters	Blows with Small Orifice				At rest		Exercise Small Orifice Blow	
Pulse Rate		1			1	2	3	Rate		Pulse Rate before	
Systolic		2		Systolic				Systolic		No. Ascents	
Diastolic		3		**T20** Seconds				Diastolic		No. Bendings	
				Maximum Systolic						Length of blow, sec.	
				Total Seconds						Pulse Rate end 1 min.	
This line for Home Office use only		% of Normal		S+						Pulse Rate end 2 min.	

Much has necessarily been left out of this article that we would have liked to include; a full discussion of the test will be found in our paper[10] to which we have previously referred. In a pamphlet recently written for our examiners are included "Percentages of Normal Vital Capacity by Height," standard number of ascents for use with the steps, detailed instructions for application of the tests and records of tests on 4 cases with our interpretation of them. We will gladly send a copy of this pamphlet to anyone sufficiently interested to ask us for it.

Summary. *It is claimed:* 1. That accurate standardization of exercise and respiratory tests are essential if comparable results are to be obtained.

2. That the effect produced by exercise is distinctly different from that due to breath holding.

3. That the instrument here described furnishes an easily portable spirometer combined with an orifice for measuring breath-holding ability at a pressure of 20 mm. Hg. and an optimum rate of flow of 36 cc. per second. Standardization of breath holding is thus effected.

4. That throughout the blow the changes in systolic pressure may be noted and evidence of the heart's response easily obtained.

5. That shortening of the blow immediately following the two-step exercise of Master and Oppenheimer, also standardized, and its rate of return are outstanding indications of circulatory fitness.

6. That vital capacity is an important index, but that the length of the small orifice blow with the systolic changes occurring during the blow and their relationships to each other are of more diagnostic and prognostic value.

7. Changes in the systolic curve during a blow are shown, probable reasons for these changes briefly referred to, a table of values presented, derived from 88 normals and tentative limits adopted between normal and subnormal responses.

BIBLIOGRAPHY.

1. Frost, H. M.: Assn. Lif Ins. Med. Dir., 1922, **9**, 207; N. E. M. Life Ins. Med., 1926, **1**, 136; Assn. Life Ins. Med. Dir., 1927, **14**, 183.

2. Master, A. M., and Oppenheimer, E. T.: Am. J. Med. Sci., 1929, **177**, 223.

3. Wells, P. V.: Review of Scientific Instruments, 1930, **1**, 332, new series.

4. Hutchinson (1846): *See* Myers: Vital Capacity of the Lungs, Williams & Wilkins, Baltimore, 1925, p. 17.

5. MacLeod, J. J. R.: Physiology and Biochemistry in Modern Medicine, 5th ed., C. V. Mosby Company, St. Louis, 1926.

6. Peabody, F. W.: J. Am. Med. Assn., 1924, **82**, 1808.

7. Myers, J. A.: Vital Capacity of the Lungs, Williams & Wilkins, Baltimore, 1925 p. 17.

8. Jackson, E. M., and Lees, H. D.: Am. J. Physiol., 1929, **87**, 654.

9. Wittich, F. W., and Polczak, J. A.: Am. Rev. Tuber., 1926, **13**, 54.

10. MacKenzie, L. F., Wells, P. V., Dewis, E. G., and Ylvisaker, L. S.: Proc. 40th Annual Meeting Assn. Life Ins. Med. Dir. of America, 1929, **16**, 36.

11. Sabrazés, J.: Gaz. Hebd. Sci. Med., Bordeaux, 1902, **23**, 99.

12. Stange, V. A.: Rusky Vratch, Petrograd, 1914, **13**, 72; Abstr. J. Am Med. Assn., April 4, 1914, p. 1132.
13. Henderson, Yandell: J. Am. Med. Assn., 1914, **63**, 318.
14. Palcso, B.: Ztschr. Kreislaufforschung, 1928, **20**, 457.
15. Bürger, M.: Klin. Wchnschr., 1926, **5**, 777, 825.
16. White, Paul D.: Am. J. Med. Sci., 1920, **159**, 966.
17. Fraser, F. R.: Lancet, 1927, i, 529, 589, 643.
18. MacKenzie, L. F.: Proc. Assn. Life Ins. Med. Dir. of America, 1922-1923, **9**, 70.

THE PRODUCTION OF HYPERTROPHIC ARTHRITIS BY INTERFERENCE WITH THE BLOOD SUPPLY.*†‡

By Arthur D. Goldhaft, V.M.D.,

Lillie M. Wright, M.A.,

and

Ralph Pemberton, M.D.,

Philadelphia.

In a series of previous contributions evidence has been adduced to indicate that interference with the blood supply in the finer vessels constitutes part of the disturbance of physiology resulting in the phenomena of arthritis and the rheumatoid syndrome. The lines of reasoning which led to this conclusion were based upon the following: Studies of the blood gases; the blood count at the periphery; the peripheral surface temperature; direct inspection of the capillaries and study of the rate of removal from the circulating blood of substances ingested by mouth under various experimental conditions involving the circulation in the limbs. These studies have been elsewhere reported in detail.[1–6] It remained, however, to test further the conclusions reached by means of more direct experimentation.

In 1909 Wollenberg[7] approached the subject of the induction of arthritis from the anatomic and orthopedic standpoints and conducted a series of experiments upon dogs in which ligation of the blood supply to the patella resulted in overgrowths of it. These observations were also elaborated by Axhausen,[8] but seem to have remained more or less buried in the literature and to have failed to exercise the influence which they should have commanded. It

* The chemical part of the work here reported is from the Laboratory of Clinical Chemistry, Presbyterian Hospital.

† The work here reported is part of a study on chronic arthritis in collaboration with Dr. Robert B. Osgood, of Boston. The expenses of the investigation were defrayed by contributions from various sources, including a number of patients.

‡ Preliminary reports of this work were made as follows: J. Michigan Med. Soc., 1927, **26**, 599; Arthritis and Rheumatoid Conditions; Their Nature and Treatment, Philadelphia, Lea & Febiger, 1929.

was decided, therefore, to repeat the experiments of Wollenberg, especially in the light of the present viewpoint, reached by a different line of investigation. Corroboration of Wollenberg's results would obviously go a long way to substantiate the conclusion above outlined.

In attempting the induction of any of the phenomena of arthritis it is important to bear certain facts in mind. Following the classical morphologic studies of Nichols and Richardson,[9] arthritis has come to be recognized in this country, and essentially also in England under different names, as presenting in general two types, namely, atrophic and hypertrophic. Nichols and Richardson called these types proliferative and degenerative respectively and specifically stressed that, while these types are apparently justified morphologically and clinically, they do not necessarily represent finality in classification, and that they exhibit, avowedly, some points of contact and apparent merger. In general, however, atrophic arthritis represents the variety seen for the most part in persons below mid-life and hypertrophic arthritis that encountered in largest measure at or beyond mid-life. Atrophic arthritis is, furthermore, generally thought to be a frequent expression of the effect of infectious factors and hypertrophic arthritis of physiologic disturbances of a more generic nature, such as those referable to age, trauma, the climacteric and the like. Some students of the subject have dogmatized rather strongly as to the invariably infectious nature of atrophic arthritis and some have denied that infection plays any etiologic rôle in hypertrophic arthritis. It can fairly be said, however, that the evidence is not so complete as to justify such dogmatism. There are undoubtedly many factors, other than infection, operative in at least a contributory sense in the induction of atrophic arthritis; there is strong evidence that at least some, possibly many, cases of hypertrophic arthritis are themselves associated with and conceivably referable to infectious agencies. This statement is believed necessary for the proper interpretation of the experimental results to be described.

The methods used were as follows: Six apparently healthy dogs were selected, of varying ages, temperature, respiration and pulse being normal. They presented no nasal discharge or conjunctivitis and bowel movement and urination were apparently normal. The animals were all given an initial bath in a 5 per cent solution of lysol to remove external parasites and were subsequently bathed in the same way twice a month during the conduction of the experiments. Microscopic examination was made of the feces in all cases for internal parasites. All dogs showed two parasites, namely, ascarides (roundworm) and hookworm. The animals were accordingly starved overnight and given tetrachlorethylene in a capsule, in the dosage of 3 cc. per 22 pounds of weight. Examination was made again in three weeks and found to be negative for ova and

parasites, and this examination was repeated at three-week intervals throughout the experiment. Twenty-four hours prior to operation under ether anesthesia a light meal, consisting of milk only, was given to each dog.

The hair in the region of the patella of the leg to be operated upon was shaved and the skin was scrubbed thoroughly with soap and water for two minutes. The region of the patella was painted with iodin, then ether, then iodin again. A pad of cotton soaked in a 5 per cent solution of lysol was placed at the site of the patella for an hour before operation. Instruments and surgical material were sterilized in the orthodox manner. The dogs were then placed under general ether anesthesia and the ensuing operation was performed, following the method of Wollenberg, with the aim of cutting off the blood supply to the patella of one leg. The other leg was left as a control. A linear longitudinal incision of 2 inches was made directly over the patella through the skin, subcutaneous tissue, and part of the deep fascia. The deep fascia was dissected so as to free the patella and the overlying and surrounding tissues. The following technique was then utilized in tying off all bloodvessels No. 12 twisted silk being employed. At a point beginning at the distal edge of the patella a row of overlapping sutures, one in advance of the other, was carried in a circuitous manner completely around the patella to the point of beginning. A second row of overlapping sutures was placed around the first row of sutures in such a manner that the loops of the second row were half way between the loops of the first row. When each suture was put in place the slack of the previous suture was taken up. The wound was closed and dressed in the usual manner. After the operation the dogs were given no food until they could lap water voluntarily. On the evening of the operation the dogs were given a light meal consisting of a cupful of milk, toast and vegetables. No weight was placed by any of the dogs for ten days on the leg operated upon. For several days there were extreme pain and lameness and also a marked edema. Ten days after the operation the wound had healed by first intention in every instance.

The arterial anastomosis around the knee joint in the human being, according to Gray,[10] is formed by branches from six arteries—the medial, lateral and highest genicular, the fibular, the descending branch of the lateral femoral circumflex and the anterior recurrent tibial arteries. In the dog, according to Dr. William Lentz, professor of anatomy at the Veterinary School of the University of Pennsylvania (personal communication), the patella and the knee joint are supplied by branches from the two anterior femoral arteries, from the articular branch of the anterior femoral artery and from the saphenous artery.

The blood supply to the patella, in this operation, was apparently completely interrupted, at least for a long time. The vessels in the

tissue surrounding the patella were tied off and those from the skin and superficial tissues were dissected away. Considering the fact that interruption of the blood flow was followed by progressive consequences as late as eight months after the operation, it is presumable that the circulation was markedly interfered with, if not entirely obstructed, until the dogs were killed. The period of most graphic and possibly most rapid change was apparently between the third and the sixth months.

An incomplete series of injection experiments suggests that a compensatory circulation may have been established to a very small degree, but this is by no means certain. In any event there can be no question that a radical reduction was achieved in respect to the amount of blood reaching the patella through the normal channels.

In one animal the control leg had been the site of a resection of the tibial nerve three months and three weeks previously, but recovery had been uneventful, complete and without lameness.

Five of the six dogs lived through the period of nine to ten months, during which the experiment lasted. Dog IV ("Brown") died accidentally four months after the blood supply to the patella had been ligated. Brief reference is later made to this animal, but the results of the operation do not justify consideration in the final conclusions.

In considering the effects of an operation of the above nature in, or near to, a joint, the possible effect of trauma of any kind in the production of an arthritis is to be borne in mind. For this reason experiments were carried out on two animals with the aim of eliminating from consideration any mechanical influence arising from the operation, or from sutures introduced, in the production of arthritic changes later to be noted. An amount of No. 12 silk, equal to that used in the ligating experiments, was placed completely around the patella at the same depth as in the experiment previously described. The silk was simply fixed in position and care was exercised to avoid tying off any bloodvessels or interfering with their blood flow. Preparation and operative technique were otherwise as described. The reaction after this operation was similar to that which followed ligation of the patellar vessels.

Protocols. Dog I.—A male, mongrel beagle hound, named "Hound," 30 pounds in weight, two years of age, with completely united epiphyses, was operated upon on January 23, 1927. The blood supply to the patella of the right leg was ligated, resulting in lameness of that leg. Roentgen rays of the leg operated upon, on the following dates, showed:

April 30: Overgrowth of the patella distally, and an indented area proximally.

July 14: A slight increase in the length of the overgrowth.

October 17: Greater increase in calcification of the overgrowth.

On November 24 the dog was sacrificed.

Examination after death showed a normal left leg, but thickening and adhesions of the fascia around the joint capsule of the right leg (the leg operated upon). The patella and sheaths were dissected from the joints and were split lengthwise. The left (normal) patella could be dissected and stripped easily and could be split only with great effort. All of the normal patellæ were easily dissected and stripped, but very difficult to split. The right patella could be dissected and stripped only with difficulty. It showed a distal overgrowth, an irregular rounded extension of the patella, 12 per cent of the length of the normal patella. The patella was discolored on its articular surface and the split surface showed areas of brown-colored tissue.

Dog II.—A female, mongrel dog, named "Wooley," 30 pounds in weight, one year of age, with completely united epiphyses, was subjected to the same operation upon the right leg on January 23, 1927. Roentgen rays of the leg operated upon, on the following dates, showed:

April 30: A slight overgrowth of the patella distally, and a small indented area proximally.

July 14: An increase in the overgrowth and in the calcification of the overgrowth as well as in the area of identation.

October 17: A greater calcification of the overgrowth.

On October 17 the dog was sacrificed.

Examination after death showed a normal left leg, but thickening and adhesions around the right joint and capsule. The left (normal) patella could be dissected and stripped easily and clearly. It was shiny, smooth and white on its articular surface, as were all normal patellæ. The right patella (the patella operated upon) could be dissected and stripped with great difficulty only. It showed a distal overgrowth, a fully rounded extension of the patella, 53 per cent of the length of the normal patella. The overgrowth was entirely covered with fascia and, on beginning dissection, it was difficult to tell where the overgrowth ended and the tendon sheath began. The nonarticular surface of the patella had several knobby, bony, fragile growths. The articular surface was darker in color than the normal.

Dog III.—A male, mongrel Irish terrier, named "Irish," 25 pounds in weight, one and a half years of age, with completely united epiphyses, was operated upon on May 15, 1927. The blood supply to the patella of the left leg was ligated, resulting in lameness of that leg.

This dog had been subjected to a nerve resection of the right leg on January 23 without any apparent change from the normal as to function. This leg was used as the control.

Roentgen rays of the left leg on the following dates, showed:

July 14: An overgrowth of the patella distally.

October 17: An increase in the overgrowth and in the calcification of the overgrowth, and an indented area proximally.

February 27, 1928: Slight further increase in the overgrowth.

On February 27 the dog was sacrificed.

Examination after death showed an apparently normal right leg and joint, but thickening and adhesion of the fascia around the joint of the left leg (the side of the ligation) with several small injuries on the condyles of the left femur. On observation, the right patella appeared normal, but it could not be dissected as easily as the other two normal patellæ. The left patella (the side of the ligation) could be dissected and stripped with great difficulty only. It showed a distal, spear-head-shaped overgrowth, 50 per cent of the length of the normal patella. The overgrowth was entirely covered with fascia and, on beginning dissection, it was difficult to tell where the overgrowth ended and the tendon sheath began. Its articular surface

was darker in color than that of the normal. Near the proximal end of the articular surface each patella showed a broad, shallow groove which was probably a congenital deformity.

Dog IV.—A male, mongrel beagle hound, named "Brown," 25 pounds in weight, two and a half years of age, with completely united epiphyses, was operated upon as a control on February 5, 1928. In this operation sutures were inserted around the patella of the right leg, but the blood supply was not tied off. Recovery was complete and without lameness. Roentgen rays of the right leg on May 10 and July 12 showed no change from the normal.

On August 1 the blood supply to the patella of the left leg was ligated, resulting in lameness of the leg operated upon. Roentgen rays of the left leg on September 27 and December 13 showed no change from the normal. On December 12 "Brown" died from malnutrition following a severe gastro-enteritis, probably due to eating chicken feed composed of meat scraps, bran, middlings and corn meal.

Examination after death showed an apparently normal right leg and joint, but thickening and adhesions of the fascia around the left joint (the side of the ligation), marked injuries to the left femur and a deformed articular surface of the left patella with overgrowth of the articular cartilage centrally. The left patella was 1 cm. nearer the tibia than the right patella. Roentgen rays after partial dissection showed a change in shape of the left patella, but no overgrowth. The right patella could not be dissected or stripped as easily as could the two normal patellæ, because of the slight amount of thickening and adhesions of the surrounding tissues due to the control operation. It could be split without great effort. The left patella (the side of the ligation) could be dissected and stripped only with difficulty and also could be split very easily. It showed no overgrowth, although it did show a change in shape. The articular surface was somewhat shiny and smooth, but darker in color than normal patellæ.

Dog V.—A male, mongrel, beagle hound, named "Yellow," 25 pounds in weight, two and a half years of age, with completely united epiphyses, was operated upon as a control on February 5, 1928. In this operation sutures were inserted around the patella of the right leg, but the blood supply was not tied off. Recovery was complete and without lameness.

Roentgen rays of the right leg on May 10 and July 12 showed no change from the normal.

On August 1 the blood supply to the patella of the left leg was ligated, resulting in lameness of the leg operated upon.

Roentgen rays of the left leg, on the following dates, showed:

September 27: A change in shape, a beginning distal overgrowth, and a fuzzy appearance of the patella.

January 10, 1929: Increased overgrowth of the patella.

April 4: A slight increase in the overgrowth and in the calcification of the overgrowth.

May 17: A slight increase in the length, in the width and in the calcification of the overgrowth.

On January 10 a skin or surface infection of the left leg was noticed, caused apparently by the rubbing of the chain with which the dog was tied. There was no fever, swelling, lameness or pain. No complications developed. The infection healed in ten days under treatment with a 1 per cent solution of chloramin-T (Squibbs' Dakin-Carrel solution).

On May 17 the dog was sacrificed.

Examination after death showed an apparently normal right leg, but much thickening and many adhesions of the fascia around the left joint

(the side of the ligation) and marked erosion of the condyles of the left femur. The right patella appeared normal, although it could not be dissected and stripped as easily as a normal patella, because of the slight amount of thickening and adhesions of the surrounding tissue due to the control operation. Also there were several fragile areas present on the nonarticular surface. The left patella (the side of the ligation) could be easily split, and could be dissected and stripped only with difficulty. It showed a distal overgrowth, a fully rounded extension of the patella, 31 per cent of the length of the normal patella. On beginning dissection it was difficult to tell where the overgrowth ended and the tendon sheath began. The nonarticular surface was knobby. The articular surface was somewhat shiny and smooth.

Dog VI.—A male, mongrel collie dog, named "Collie," 20 pounds in weight, eight months of age, with epiphyses not united, was operated upon on August 14, 1928. The blood supply to the patella of the left leg was ligated, resulting in lameness of the leg operated upon.

Roentgen rays of the leg operated upon, on the following dates, showed:

September 27: A very small overgrowth distally and a small indented area proximally with an increase in the calcification of the patella.

January 10, 1929: A very slight further increase in the overgrowth.

April 4: A very small further increase in the overgrowth.

May 17: No change from the Roentgen ray of April 4.

On May 17 the dog was sacrificed.

Examination after death showed a normal right leg and patella, but thickening and adhesions of the fascia surrounding the left joint, a slight injury on the condyles of the left femur, a deformed articular surface of the left patella and overgrowth centrally of the articular cartilage of the left patella. The left patella could be dissected and stripped with only a slight amount of difficulty, and could be split easily. It showed a distal overgrowth, a rounded extension of the patella, 11 per cent of the length of the normal patella. On beginning dissection it was rather difficult to tell where the overgrowth ended and the tendon sheath began. The patella appeared somewhat smooth and shiny on its articular surface.

The above experiments show clearly that at the end of a period of from nine to ten months definite and considerable overgrowth of the patella had taken place in every dog following interference with the blood supply to that region. In the animals in which nonabsorbable suture material in equal amount had been placed around the patella following an otherwise identical operation, no observable overgrowth of the patella took place. There was possibly a slight increase in density at the distal end of the patella of "Yellow," but the contrast between these two sets of animals was beyond all possibility of error. In all dogs, including the controls, in which silk ligature had been placed as a foreign body, there was a certain amount of thickening and adhesion of the structures in the neighborhood of the patella tendon and the joint capsule. This was most marked in the animals in which the blood supply had been interfered with and resembled grossly the arthritic changes observed in human beings in the so-called "periarticular" structures. The most graphic changes in these last-mentioned animals were in connection with the patella, which showed unmistakable overgrowth of marked and

varying degree. The first evidences of this were to be seen upon Roentgen ray examination two to three months after the operation. (The left patella of the dog "Brown," at the time of death, four months after ligating the blood supply to it, showed no overgrowth, but did show a slight change in shape.) In all dogs which lived as long as nine or ten months the overgrowth varied in size from one-ninth to more than one-half that of the original patella itself. Three of the 5 dogs showed overgrowths of 31, 50 and 53 per cent of the size of the normal patellæ. The other 2 dogs showed overgrowths of 11 and 12 per cent of the size of the normal patellæ. "Collie" (Dog VI), the dog that showed the least overgrowth, was very young, being eight months of age at the beginning of the experiment. "Hound" (Dog I), the dog that showed an overgrowth of 12 per cent, was one of the oldest animals. It is interesting to observe that, whereas there was a considerable amount of thickening and adhesion of the associated structures, the overgrowth of the patella was apparently entirely discrete. In the Roentgen ray plates in no instance did it merge more or less gradually into the attached tedinous tissue as one might possibly have expected. Roentgen ray study suggests, in some cases, that the overgrowth of the patella began by means of scattered areas of calcified matter of varying density within the limits of what proved later to be the overgrowth itself. Later, the advancing edge of the new growth of the patella became characterized by what appeared to be a definite line of limitation, almost as though a membrane had enclosed it. On dissection, nine or ten months after the operation, however, this was not so apparent. The shape of the forward projection varied between a pointed spear-head-shaped overgrowth and a fully rounded extension of the patellar bone itself. As growth proceeded, the structure of the overgrowth, light at first, as shown by the Roentgen rays, became denser, obviously due to increasing impregnation with osseous salts.

It is obvious that operative infection might be suspected of contributing to the results achieved. This explanation is unlikely, however, in view of the fact that the dogs showed no evidence of infection locally or systemically or at autopsy. Furthermore, essentially the same technique was used in the control animals which showed none of the changes above described. It is to be noted that, in the appended report on microscopic findings, there was "no sign of acute inflammation or necrosis."

Histologic study of one such typical specimen was kindly made by Dr. Edward Krumbhaar, professor of pathology at the University of Pennsylvania, who reported as follows:

"As compared with the normal patella, the experimental patella, cut in longitudinal section, is prolonged at one end to a point of dense tissue visible to the naked eye. Under the microscope this is seen to merge imperceptibly with the true bone. At its distal end it is composed of dense, relatively

acellular, pale pink staining material, with long thin nuclei, many of which lie on the edge of thin narrow slits. As the normal bone is approached, these spaces become more numerous and more oval, with the cell lying more in the lumen, until finally the ordinary bone cell in its space predominates. On the side of the articulation it is bounded by fibrous tissue, which persists until the synovium and cartilage is reached. On the other side the osteoid tissue extends well past the level that is true spongy bone, eventually to merge with its periosteum. The fatty tissue between the bone spicules contains definitely more cells than in the control; that is more lymphocytes, plasma cells and possibly hemopoietic cells, such as neutrophils. There is no sign of acute inflammation or necrosis. DIAGNOSIS—OSTEOID TRANSFORMATION OF TENDON, BEGINNING MYELOID ACTIVITY?"

The fundamental processes concerned in the development and overgrowth of bone, physiologic and pathologic, are by no means clearly understood. Importance would be attached to fuller knowledge of the chemical changes taking place in respect to the mineral salts, chiefly calcium and magnesium, and also the phosphorus, in experiments such as the above. Analyses were accordingly undertaken, with the coöperation of Dr. F. A. Cajori, upon the newgrowth, upon the original portion of the patella operated upon and upon the patella of the control side. These analyses included the total ash, calcium, magnesium and phosphorus content. The total ash of the patella tendon sheath was also determined.

The patella was divided longitudinally to provide portions for section and for chemical analysis. The halves for chemical study were further divided into the original patella and the overgrowth. These were then dried at 100° C. to constant weight and ashed in a platinum crucible to a white ash. The ash was weighed, and then dissolved in a small amount of hydrochloric acid and made up to 100 cc. Twenty cubic centimeters were used for analysis. In the case of the ash of the overgrowth, which was dissolved in hydrochloric acid and made up to 50 cc., 10-cc. portions were used for analysis. For calcium and magnesium the method of Kramer and Howland[11] was used; for phosphorus, Brigg's[12] method for phosphorus in urine was followed.

Summary of Chemical Studies. The table on page 395 gives the results, all of which are averages of several closely agreeing analyses.

It will be seen that the operation of tying off the patella had little effect on the ash, calcium and phosphorus content of the patella. The percent of magnesium is increased, however, in the ash of the patella of the side operated upon, and especially in the ash of the newgrowth (overgrowth) on that side. This overgrowth is not completely calcified, as evidenced by the fact that the overgrowth has a somewhat lower ash content than have the patellæ.

The ash content of the tendon sheaths on the side operated upon is a little higher than the ash of the tendon sheath on the control side. The small amounts of ash available for weighing after the burning of the tendon sheath and the uncertainty of clean dissection of the tendon sheath before ashing make these results less satisfactory.

	Dog.		
	"Hound."	"Wooley."	"Irish."
Ash, per cent:			
Unoperated	50.87	52.98	54.46
Operated	51.69	52.72	54.74
Overgrowth	..	44.76	
Calcium, per cent of ash:			
Unoperated	41.27	41.09	40.62
Operated	41.35	40.41	40.32
Overgrowth	..	41.52	
Phosphorus, per cent of ash:			
Unoperated	17.10	17.65	17.50
Operated	17.97	17.85	17.41
Overgrowth	..	18.03	
Magnesium, per cent of ash:			
Unoperated	0.54	0.51	0.65
Operated	0.67	0.65	0.66
Overgrowth	..	0.92	
Tendon sheath, per cent of ash:			
Unoperated	1.75	1.82	0.55
Operated	2.15	2.23	0.53

The above analytical results apply to the first two dogs only. The patellæ of "Irish" (Dog III) do not differ with respect to magnesium. In the ash of both patellæ the per cent of magnesium is high, similar to the magnesium content of the patellæ on the side operated upon of the other two dogs. It should be noted, however, that "Irish," in contrast to the other two, had had a nerve resection on the leg which later served as the control in the experiments on ligating the patellæ.

An increase in the magnesium in bone has been noted by others in abnormal bone conditions. McCrudden[13] found an actual increase in magnesium in the bones in osteomalacia. Gassman[14] reports finding increased magnesium in rachitic bone, and Toverud[15] found an increase of magnesium in the teeth of Howe's guinea pigs with chronic scurvy.

It may be concluded that the derangement in bone metabolism following the tying off of the circulation to the patella brings about a condition seen also in certain pathologic states affecting bones, in which magnesium is deposited in greater amounts than normally takes place.

Discussion. Taken in conjunction with the work of Wollenberg, these experiments admit of no doubt that at least some of the characteristic bony changes of arthritis can be induced by interference with the blood supply. The type of arthritis which, obviously, is most strongly suggested in these experimental results is hypertrophic arthritis. It would be a mistake, perhaps, to suppose that only hypertrophic manifestations can be brought about by this measure. There are apparently a few areas to be observed in the specimens in which a certain amount of erosion or atrophy suggests the atrophic type. The phenomenon of overgrowth of bone or atrophy of bone is not necessarily the only definitive feature of one or the other kind

of arthritis. Leriche and Policard[16] state that "bone resorption and osteogenesis appear indissolubly linked" and that "it is exceptional to find bone rarefaction without noting in the vicinity a certain degree of new bone formation." Many cases of atrophic arthritis are accompanied by some overgrowth of bone. In other experiments in process of being reported by the writer and his associates the evidence is strong that disturbance of the blood supply in the direction of vasoconstriction is most marked in atrophic arthritis, although well marked also in hypertrophic arthritis.

The subject of morphology of bone which had perhaps reached a rather inactive condition has recently been opened up, partly through the stimulating work of Leriche and Policard. No attempt will be made here to discuss this large field beyond stating that these authors have shown that older conceptions in this connection may require some revision. These workers have reached a conclusion as regards normal bone which is in close rapport with the conclusions reached by the present writer and his associates in relation to arthritis. Thus, Leriche and Policard advance, as a thesis fundamental to an understanding of osteogenesis, the general principle that activity of the circulation tends toward rarefaction of bone, and, conversely, that stasis of the circulation favors ossification. This latter is in striking agreement with the work here reported. Therefore, while the results of the experiments here described resemble closely the phenomena of hypertrophic arthritis, the writers do not mean to indicate that the processes concerned are confined solely to that variety. They believe, indeed, that they may also operate under somewhat different conditions in atrophic arthritis.

The incidence of positive results in the present series was very high. It is entirely conceivable that at the hands of others or at the hands of the present workers in another series, the proportion of positive results might be lower. The main point at issue is, not that the results described will invariably follow the above operative procedure, because the present series is too small to admit of such a conclusion, but that in at least a definite proportion of cases interference with the blood supply is followed by overgrowth of bone.

In describing experiments designed to elucidate the pathologic background productive of arthritis and rheumatoid phenomena, it seems necessary to point out that the changes in physiology observed are not out of consonance with the recognized influence of infection in many cases of arthritis. The belief that all cases of arthritis are due only to infection is so frequently to be met, among those who are not studying the disease intensively, that the necessary link between even a definitely causative infection and the end result, arthritis, is largely overlooked. The most cursory survey of the problem will indicate that there must be a medium, or chain of disturbances, through which such infection, when operative, expresses itself. Accepting the premise that many cases of arthritis are precipitated by infection and that many other factors are opera-

FIG. 1.—Roentgen ray showing the normal patella of dog "Irish." (The shadow behind the patella is the condyle.) The Roentgen ray was taken before the ligation of the patellar vessels.

FIG. 2.—Roentgen ray showing the overgrowth of the patella of dog "Irish," two months after ligation of the patellar vessels.

FIG. 3.—Roentgen ray showing the overgrowth of the patella of dog "Irish." Nine and a half months after ligation of the patellar vessels.

FIG. 4.—Roentgen ray showing the normal patella of the dog "Wooley." (The shadow behind the patella is the condyle.)

FIG. 5.—Roentgen ray showing the overgrowth of the patella of dog "Wooley" three months after ligation of the patellar vessels.

FIG. 6.—Roentgen ray showing the overgrowth of the patella of dog "Wooley" nine months after ligation of the patellar vessels.

FIG. 7.—Roentgen ray showing the normal patella of dog "Yellow." The Roentgen ray was taken before the ligation of the patellar vessels.

FIG. 8.—Roentgen ray showing the overgrowth of the patella of dog "Yellow" two months after ligation of the patellar vessels.

FIG. 9.—Roentgen ray showing the overgrowth of the patella of dog "Yellow" five months after ligation of the patellar vessels.

FIG. 10.—Roentgen ray showing the overgrowth of the patella of dog "Yellow" nine and a half months after ligation of the patellar vessels.

FIG. 11.—Roentgen ray showing the normal patella of dog "Yellow." (The shadow behind the patella is the condyle.)

FIG. 12.—Roentgen ray showing the patella of dog "Yellow" five months after the control operation. The Roentgen ray shows no noteworthy change from the normal.

FIG. 13.—Roentgen ray showing the patella of dog "Yellow" one year and three and a half months after the control operation. The Roentgen ray shows no noteworthy change from the normal.

FIG. 14.—Roentgen ray showing the normal patella of dog "Brown." (The shadow behind the patella is the condyle.)

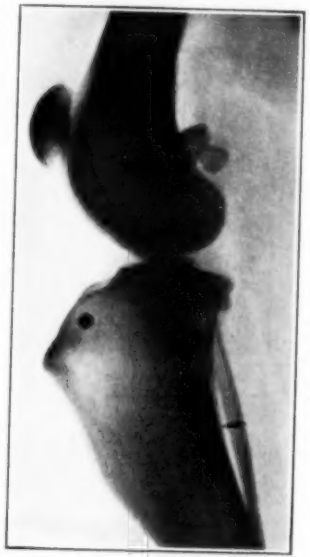


FIG. 15.—Roentgen ray showing the patella of dog "Brown" three months after the control operation. The Roentgen ray shows no change from the normal.

FIG. 16.—Roentgen ray of the patella of dog "Brown" seven and a half months after the control operation. The Roentgen ray shows no change from the normal.

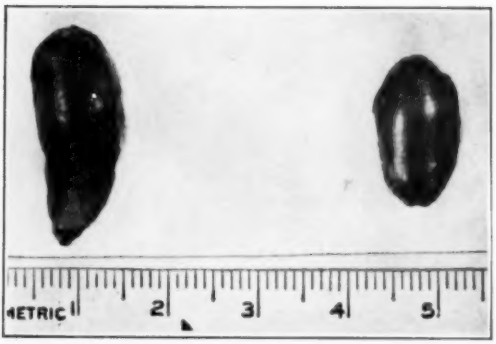


FIG. 17.—Photograph showing the overgrowth of the patella of dog "Irish" nine and a half months after ligation of the patellar vessels. The lower portion of the left patella shows the overgrowth.

FIG. 18.—Photograph showing the overgrowth of the patella of dog "Wooley" nine months after ligation of the patellar vessels. The lower portion of the right patella shows the overgrowth.

tive in the production of both atrophic and hypertrophic arthritis, the experiments here discussed throw light upon the intermediary mechanism by which the phenomena of the rheumatoid syndrome are brought about, both in the soft and in the bony tissue.

Conclusions. Experiments are reported in which the phenomena of arthritis, chiefly of the hypertrophic variety, are brought about in the region of the patella of dogs by ligation of the blood supply to the patella. Control experiments in which an amount of silk ligature equal to that used in the original experiments was placed around the patella, following upon an otherwise essentially identical operation, failed to produce any overgrowth after a comparable lapse of time.

Analyses of the overgrowth and of the original patella giving rise to the overgrowth show that the percentage magnesium content in these tissues is higher than on the control side. The involvement of the mineral metabolism in the region affected is thus clearly indicated.

These experiments are in entire consonance with those arrived at, following a different line of reasoning, by Wollenberg and indicate beyond any reasonable doubt that disturbance of the blood supply must henceforth be regarded as one of the factors capable of producing arthritic change. Taken in conjunction with other work referred to early in the present text, these experiments afford strong evidence that interference with the blood supply, probably in the nature of vasoconstriction, constitutes at least a part, probably a large part, of the underlying physiologic disturbance productive of the phenomena of chronic arthritis, especially the hypertrophic type as encountered in human beings.

REFERENCES.

1. Pemberton, R., Hendrix, B. M., and Crouter, C. Y.: Studies in Arthritis; the Blood Gases and the Blood Flow, J. Metab. Res., 1922, **2**, 301.
2. Peirce, E. G., and Pemberton, R.: The Red Cell Count in Arthritis, Arch. Int. Med., 1927, **39**, 421.
3. Cajori, F. A., and Crouter, C. Y.: The Red Cell Count in Arthritis, Arch. Int. Med., 1927, **39**, 429.
4. Wright, L. M., and Pemberton, R.: The Peripheral Surface Temperature in Arthritis, Arch. Int. Med. 1930, **45**, 147.
5. Pemberton, R., Cajori, F. A., and Crouter, C. Y.: The Effect of Changes in the Circulation on Carbohydrate Utilization, J. Biol. Chem., 1925, **66**, 89.
6. Pemberton, R.: Arthritis and Rheumatoid Conditions; Their Nature and Treatment, Philadelphia, Lea & Febiger, 1929, p. 115.
7. Wollenberg: Arch. f. Orth. u. Mechano. Umfall. Chir., 1909, **7**, 226.
8. Axhausen, G.: Ztschr. f. Orth. Chir., 1913, **33**, 223.
9. Nichols, E. H., and Richardson, F. L.: J. Med. Res., 1909, **21**, 149.
10. Gray, H.: Anatomy, Descriptive and Applied, 23d ed., London, Longmans, Green & Co., Ltd., 1926, p. 713.
11. Kramer, B., and Howland, J.: J. Biol. Chem., 1926, **68**, 711.
12. Briggs, A. P.: J. Biol. Chem., 1922, **53**, 13.
13. McCrudden, F. H.: J. Biol. Chem., 1910, **7**, 199.
14. Gassman, T.: Ztschr. f. Physiol. Chem., 1910, **70**, 161.
15. Toverud, G.: J. Biol. Chem., 1923, **58**, 583.
16. Lerich and Policard, translated by Moore and Key: The Normal and Pathological Physiology of Bone, St. Louis, C. V. Mosby Company, 1928, p. 66.

SUBPHRENIC ABSCESS.*

By Gatewood, M.D.,

ASSOCIATE CLINICAL PROFESSOR OF SURGERY, RUSH MEDICAL COLLEGE OF THE UNIVERSITY OF CHICAGO, CHICAGO, ILL.

(From the Presbyterian Hospital of Chicago and the Surgical Department of Rush Medical College of the University of Chicago.)

Although subphrenic abscess was described by Barlow[1] in 1845, it was not until 1879 that the first operation for this condition was done by von Volkmann.[2] During the past few years, this subject has been studied extensively and as a result much earlier recognition has been possible. Despite this and the development of better operative technique, the mortality has not been correspondingly lowered. According to Moynihan,[3] we should expect about 16 per cent mortality. Lockwood's[4] statistics from The Mayo Clinic gave a mortality of 33.3 per cent in 81 operated cases, with a mortality of 97 per cent in 32 unoperated cases, and Barnard's[5] original group of 76 cases collected from London hospitals has a death rate of 47 per cent. In a group of 41 cases occurring in the Presbyterian Hospital during the past ten years, the mortality rate is 34 per cent if 3 cases in which no operation was performed are included, or 29 per cent in the operated cases. Sachs[6] states that in the first three weeks 15 per cent die, but that after this time, the mortality is 50 per cent. His mortality in the unoperated cases was 71.5 per cent and Elsberg's[7] was 82 per cent.

Etiology. All subphrenic abscesses must be either *primary* or *secondary*. True primary abscesses must be very few and these are probably limited to traumatic infections such as stab wounds, although Lee[8] has called attention to cases of "spontaneous origin" and a number of idiopathic cases have been reported.

The *secondary* subphrenic abscesses form the great group most frequently encountered by the surgeon. They are the result of (1) direct extension from a neighboring primary focus, or of (2) lymphogenous infection from a more remote source, or of (3) blood-stream infection. Naturally, most subphrenic abscesses are the result of *direct spread* of the infection, from such sources as a perforation of the stomach, appendix or gall bladder, or they form as a walled-off abscess in general peritonitis.

The relative frequency of these primary sources as the causative factor varies with the type of patient seen in the individual clinic, although in most series perforation of the stomach heads the list, and appendicitis follows closely. Even today with the earlier diag-

* Read at the meeting of the Western Surgical Association, December 13, 1929, Del Monte, Calif.

nosis and operation of appendicitis, it still remains high in the list of etiologic factors. Russell[9] (1929) reviewing 24 cases from the Postgraduate Hospital in New York, found more from the appendix and biliary tracts than from the stomach and duodenum.

It is frequently difficult to exclude other methods of infection, but there is no doubt that the *lymphatics* can carry infection to the subphrenic space in the same way that carcinomatous involvement occurs on the under surface of the diaphragm. The lymphatic connections between the subphrenic spaces and the abdominal viscera, according to Dexter,[10] are threefold: (1) The retroperitoneal cellular tissue; (2) from around the epigastric artery to the falciform ligament, which is in close association with the lymphatics of the appendix and colon, and (3) the subphrenic lymph spaces which pass through the diaphragm, connecting with the pleural plexus of lymphatics. Although infection usually travels from below upward, it may proceed from the pleural cavity downward. In 190 cases of empyema observed by Beye,[11] secondary abdominal infection was encountered in only one case. On the other hand, there were 9 cases of empyema secondary to subphrenic abscess.

Blood-stream infections usually are the result of thrombophlebitis secondary to appendicitis, diverticulitis or some other infected abdominal viscus. Rarely are they secondary to remote foci, such as boils. Metastatic liver abscess with subsequent rupture into the subphrenic space must be a much more common sequence of events than direct hematogenous infection of the subphrenic space.

The primary foci of the subphrenic abscesses observed at the Presbyterian Hospital in the past ten years have been classified as follows:

1. Stomach and duodenum, 14 cases
   - Perforated ulcer, 12
   - Perforated carcinoma, 2
2. Appendix, 10 cases
   - Direct extensions
     - Intraäbdominal*
     - Extraäbdominal (extraperitoneal)
   - Lymphatic
   - Hematogenous
3. Liver and bile passages, 7 cases
   - Suppurative cholecystitis, 5
   - Suppurative cholangeitis
   - Liver abscesses
     - Multiple—secondary to pylephlebitis, 1
     - Single—pyogenic and amebic echinococcus, 1
4. Kidney (perinephritic abscess), 3 cases.
5. Pancreas, 1 case.
6. Other infected abdominal viscera and localized abscesses as diverticulitis, 1 case; pelvic infections, etc., 4 cases.
7. Thoracic infections, chiefly empyema, 1 case.
8. Remote causes, 1 case (carbuncle of neck).

* It has been impossible to determine the exact route the infection has taken in these cases.

CHART.

Case.	Sex.	Age.	Location.	Etiology.	Complications.	Duration before operation.	Outcome.
1. 88812 . . .	Male	15	Right	Suppurative appendicitis (abdominal drainage)	.....	21 months	Cured
2. 93418 . . .	Male	39	Right	Ruptured appendix	Right-sided empyema	3 weeks (after operation, 6 years)	Cured
3. 94092* . . .	Female	30	Right	Appendiceal abscess	.....	Indeterminate	Cured
4. 98101 . . .	Female	38	Right	Echinococcus cyst of liver	.....	12 days	Cured
5. 105507 . . .	Male	49	Multiple	Perforated duodenal ulcer	Severe diabetes	4 weeks (no operation)	Died
6. 108975 . . .	Male	41	Right	Suppurative appendicitis (ruptured)	.....	3 weeks	Cured
7. 121981 . . .	Female	45	Right	Perforated gastric ulcer	Pelvic abscess	27 days	Cured
8. 133863 . . .	Male	29	Right	Appendicitis	Empyema	3 months	Died
9. 135068 . . .	Male	11	Extraperitoneal (central)	Appendicitis	.....	5 weeks	Cured
10. 143116 . . .	Male	32	Right	Carbuncle on neck	.....	10 days	Cured
11. 150252 . . .	Female	29	Right	Acute appendicitis	Empyema	2½ months	Improved
12. 153395 . . .	Male	57	Right	Actinomycosis	.....	Unknown	Improved
13. 158696 . . .	Male	44	Right	Hydronephrosis, renal calculus	Postoperative sepsis	4 weeks	Cured
14. 176200 . . .	Male	46	Left	Perforated duodenal ulcer	Suppurative pylethrombophlebitis, localized pelvic abscess	2 months (no operation)	Died
15. 177257† . . .	Female	45	Right	Cholelithiasis and biliary fistula	.....	11 months	Died
16. 177477 . . .	Female	36	Right	Ruptured appendix	Postoperative bronchial pneumonia	5 days	Died
17. 179076‡ . . .	Female	38	Left	Perforation of esophagus	Carcinoma of cardiac orifice	24 days	Improved
18. 184225§ . . .	Male	35	Right	Cholelithiasis, cholecystitis, ruptured gall bladder	.....	Unknown	Cured
19. 190404 . . .	Female	51	Right	Hysterectomy	.....	3 weeks	Cured
20. 190989 . . .	Male	35	Left	Stab wound followed by left-sided pelvic abscess	Empyema and pulmonary embolism	10 weeks	Died

21.	191437	Female	18	Left	Renal tuberculosis, perirenal abscess	.....	26 days	Cured
22.	194545	Male	42	Right	Perforated duodenal ulcer	Pleurisy with effusion	6 months	Cured
23.	196523	Male	42	Right	Probably gall-bladder disease	Pyopneumothorax	Unknown	Died
24.	197495	Female	50	Left	Diverticulitis, hernia of diaphragm	.....	.....	Cured
25.	199720‖	Male	8	Left	Empyema	Perforation of diaphragm	20 days	Cured
26.	202987	Female	24	Right	Appendicitis	Lung abscess	4½ months	Improved
27.	204824	Female	27	Right	Chronic cholecystitis	Multiple abscesses of liver, diabetes	3 weeks (no operation)	Died
28.	205438	Female	33	Right	Perforated duodenal ulcer	Duodenal fistula	36 hours	Died 17 days after operation
29.	205757**	Male	52	Right	Perforated gastric ulcer	.....	6 months	Died
30.	208267	Male	51	Right	Perforated ulcer	Retroperitoneal infection	6 weeks	Died
31.	212982	Male	46	Left	Carcinoma of stomach with perforation	Peritonitis	Unknown, short	Died at end of 10 days
32.	214407	Male	52	Right	Herniotomy	Paralytic ileus	4 weeks	Improved
33.	219916	Female	60	Right	Cholecystitis (postoperative)	.....	8 days	Cured
34.	222128	Male	31	Right	Perforated ulcer	.....	14 hours	Cured
35.	223138	Male	48	Right	Perforated ulcer	.....	About 10 days	Cured
36.	228863	Male	40	Left	Perforated ulcer	Right-sided empyema	About 4 weeks	Died
37.	229962††	Female	23	Right	Pyelitis of pregnancy	Pleural effusion	20 days	Cured
38.	230871	Male	42	Right	Perforated ulcer	Liver abscess	15 days	Cured
39.	233492	Male	35	Right	Perforated duodenal ulcer	Right-sided empyema	14 days	Died
40.	236974	Female	56	Right	Cholelithiasis, cholecystitis	.....	16 days	Cured
41.	X54438	Female	30	Left	Pancreatitis	Cholecystitis	3 weeks	Cured

NOTE.—Cures are indicated where the ultimate result is known. Those marked improved have not been followed since they left the hospital, or are not well.

* Appendiceal abscess drained four years previously. Appendiceal fistula preceding abscess. Acute.

† Subphrenic secondary to operation to close fistula.

‡ Recovered from subphrenic. Died 14 months later.

§ Transpleural drainage.

‖ Fluoroscopy shows no movement of the diaphragm on the left side.

** Empyema developed 5 weeks after operation followed by lung abscess and bronchial fistula.

†† Transpleural drainage in the anterior axillary line.

The *pathology* is that of an abscess in areolar tissues or of localized peritonitis. The abscesses are either *acute* or *chronic*. The latter may not be recognized for weeks, months or even a year or more, and cause the greatest difficulty in diagnosis. In one of our cases, four years lapsed between the primary and the secondary operation. Perforation into a viscus is rare, but may occur into the stomach, the colon, the pleural cavity, the pericardium, or even into a bronchus. Spontaneous rupture through the abdominal wall formerly was not uncommon, but is now quite rare. Various organisms have been found, the colon bacillus being present in the great majority of cases. The gas found in one-third (Lockwood) to one-fourth (Ullman and Levy[12]) of cases is usually the result of bacterial action.

Much discussion of the subphrenic spaces has led to various subdivisions, largely on anatomic grounds. Nather[13] has divided the suphrenic space into supra- and subhepatic divisions limiting the inferior border to the transverse colon and mesocolon. The spaces above the liver may be divided into right and left by the falciform ligament and these in turn into the large anterior and small posterior by the coronary ligaments. In addition to these intraperitoneal spaces, extraperitoneal infections occurring between the reflected peritoneal borders of the coronary and falciform ligaments have been described by Braun. In our present series we have not included subhepatic abscesses as suggested by Nather and it has been impossible to classify the cases except as right sided or left sided with one extraperitoneal abscess. There are 30 on the right side, 9 on the left, one multiple and one extraperitoneal (central).

Diagnosis in the early cases ordinarily is not difficult, although 2 of our patients came to autopsy without the condition being recognized and a third, though suspected, was not operated upon. As Tuft,[14] says, "suspect subphrenic in all postoperative patients who are not doing well." The history is all important, especially in the older cases, where the diagnosis may be exceedingly difficult. Although the onset usually is insidious, Fagge[15] calls attention to the fact that in some cases the symptoms begin abruptly. The patient looks and feels sick. Fever, chills and sweats are significant. The temperature is usually of the church-steeple character, suggesting pus under tension. The respiratory rate may not be in keeping with the temperature. Hiccough is always a suspicious sign although it occurs in only about a half of the cases. A cough as the result of diaphragmatic irritation has been mentioned by a number of authors but has been present in but few of our cases. Shortness of breath and difficulty in breathing vary with the amount of compression of the lung and with the amount of secondary pulmonary involvement. Epigastric pain may be marked or very slight, but subcostal tenderness is usually present. Pain in the root of the neck is frequently present.

FIG. 1.—Case No. 222128. Subphrenic abscess showing elevation of right diaphragm with fluid level and gas bubble above it.

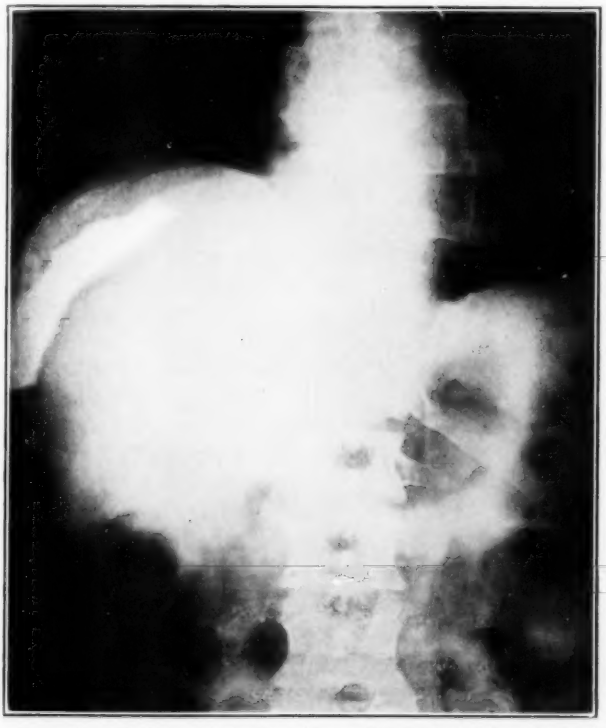


FIG. 2.—Case No. 223138. Subphrenic abscess demonstrated by lipiodol injection.

Subphrenic abscess must be differentiated from empyema, liver abscesses and neoplasms, and perinephritic abscess. This can usually be done by obtaining a good history, especially with reference to a possible primary focus, by accurate physical findings and careful Roentgen ray examination.

Physical examination reveals a sick individual with flatness as a rule on the infected side due to the elevation of the diaphragm. Older observers stress the presence of breath sounds through this flattened area but compression of the lung and the presence of fluid in the pleural cavity make this sign difficult to elicit and rather unreliable. Air in the abscess cavity may give a tympanitic note instead of the flatness and on the left side gastric tympany may complicate the picture. Tuft calls attention to the fact that the heart may be displaced upward but not laterally. Bulging in the epigastrium or on the infected side in the region of the lower ribs occurs in most late cases. Edema and redness of the overlying skin is frequently observed. The liver is usually displaced downward. The leukocyte count varies from 16,000 to 40,000, being highest in those cases complicated by liver abscess. The Roentgen ray gives us the most important information upon which to base our diagnosis. Fluoroscopically, the diaphragm on the infected side is smoothly elevated as contrasted with the irregularities due to old pleural adhesions or to the nodular irregularities of metastatic liver carcinoma and liver abscess. The splinting of the diaphragm is very noticeable and much more marked than in diaphragmatic paralysis or in lesions of the liver. Pancoast[16] believes that careful Roentgen ray examination should enable one to differentiate a subphrenic abscess from liver abscess, gumma, or from intrahepatic tumors. Paolini and D'Istria[17] report a case diagnosed by pneumoperitoneum and agree with Sante[18] upon its value as an aid. I should hesitate to use this method and Pancoast does not think it is of great value. Careful study of the films taken in the upright position often aids in the Roentgen ray diagnosis. The presence of a fluid level below the diaphragm should always be sought for but cannot be found in more than a half of the cases (Fig. 1). The cavity has been demonstrated in 3 of our cases by the injection of opaque contrast material such as lipiodol[19] (Fig. 2).

The *treatment* is essentially surgical as soon as a definite diagnosis is made. The method of approach must vary with the location of the abscess and the concomitant pathology. Statistics are of little value in determining the best method of approach and one should be governed by the findings in the individual case.

When the abscess points in the epigastrium, or in the subcostal space, drainage is best accomplished by the abdominal route. Sufficient walling off has taken place to prevent further spread provided care is exercised in exploration. The thoracic approach, either by the subpleural or transpleural method is advocated by

Lockwood and many others. It provides for a direct approach in the high-lying abscesses. Resection of the eighth or ninth rib on the right side (the seventh or eighth on the left) in the posterior axillary line, and careful suture of the pleural layers together before opening the abscess should prevent empyema, but does not in many cases. In this series of 38 cases operated upon, 27 were opened abdominally and 7 transpleurally. In 2 the subpleural method was used and in 2 a combined operation was employed. In 3 of the transpleural cases, empyema did not follow. Ochsner and Nather[20] have described a subpleural method which consists in resecting the twelfth rib and draining posteriorly above the kidney. They maintain that it permits drainage of infra- as well as suprahepatic abscesses, and that it is safer than either of the previously mentioned methods. (I have tried the method but once and failed to find the abscess which I subsequently drained abdominally.) The use of the aspirating needle has been condemned, but I have seen no harm result from the use of a moderate-sized needle, provided one is prepared to carry out what further operative technique is indicated.

Summary. 1. A review of the literature and of 41 cases observed in the Presbyterian Hospital during the past ten years, shows that the mortality in subphrenic abscess is still much too high—30 per cent or more.

2. In spite of improved diagnosis methods and earlier operation, acute appendicitis ranks high as an etiologic factor—second in our series.

3. The importance of prophylactic treatment cannot be overemphasized. Early diagnosis of appendiceal and other contributory causes and their prompt elimination will prevent the formation of many subphrenic abscesses. Adequate drainage and the adoption of the semisitting posture in all lower abdominal infections are two most important preventative measures which should not be forgotten.

4. Finally, attention is again called to the failure to consider the likelihood of subphrenic abscess in any patient not doing well after an abdominal operation, even though performed months previously.

NOTE.—I want to express my thanks to the various members of the hospital staff who have permitted me to include their cases in the compilation.

BIBLIOGRAPHY.

1. Barlow, G. H.: London Med. Gaz., 1845, **1**, 13.
2. von Volkman, R.: Quoted from Keen's Surgery, 1906, **1**, 268.
3. Moynihan, B.: Abdominal Operations, 3d ed., 1914, **1**, 149.
4. Lockwood, A. L.: Surg., Gynec. and Obst., 1921, **33**, 502.
5. Barnard, H. L.: British Med. J., 1908, i, 371.
6. Sachs, W.: Arch. f. klin. Chir., 1895, **1**, 16.
7. Elsberg, C. A.: Ann. Surg., 1901, **34**, 729.
8. Lee, R. I.: J. Am. Med. Assn., 1915, **64**, 1307.
9. Russell, T. H.: Ann. Surg., 1929, **90**, 238.
10. Dexter, R.: AM. J. MED. SCI., 1925, **170**, 810.

11. Beye, H. L.: Arch. Surg., 1927, **14**, 240.
12. Ullman, A., and Levy, C. S.: Surg., Gynec. and Obst., 1920, **31**, 594.
13. Nather, K.: Arch. f. klin. Chir., 1922, **122**, 24, abstr. J. Am. Med. Assn., 1923, **80**, 362.
14. Tuft, L.: Am. J. Med. Sci., 1925, **170**, 431.
15. Fagge, C. H.: Lancet, 1921, i, 571.
16. Pancoast, H. K.: Am. J. Roentgenol., 1926, **16**, 303.
17. Paolini, R., and D'Istria, A.: La Riforma med., 1928, **44**, 909.
18. Sante, L. R.: J. Am. Med. Assn., 1923, **80**, 464.
19. Mullen, B. P.: Surg. Clin. North America, 1929, **9**, 467.
20. Ochsner, E. W. A., and Nather, K.: Surg., Gynec. and Obst., 1923, **37**, 665.

REMOTE SYMPTOMS OF UNRECOGNIZED THYROID ADENOMATA.

With Low Basal Metabolic Rate Relieved by Operation.

By P. K. Gilman, M.D.,

clinical professor of surgery, stanford university medical school,

and

W. E. Kay, M.D.,

clinical instructor of medicine; chief of endocrinology, stanford university medical school, san francisco, calif.

During the past four years a number of private patients have presented themselves complaining of symptoms that had previously led to various diagnoses by competent physicians. Our interest in diseases of the thyroid gland led us to what we think is the correct explanation of these symptoms. In some of these cases, in spite of this special interest, the diagnosis remained obscure for some time and was then stumbled upon more or less accidentally. With the above in mind we made a careful search of the clinic records of the past ten years at Stanford University Medical School and were unable to find any case for inclusion in this report. Apparently such cases were not recognized.

In the patients reported in this paper the classical signs of thyroid toxicity were for the most part absent. Furthermore the basal metabolic rate in each instance was either normal or below normal. In many instances the patients were more or less indefinite in their complaints but were unanimous in stating that they did not feel well and knew something was definitely wrong.

Thirteen cases coming to us during the past four years furnished material for this report. Their symptoms largely directed attention away from the thyroid gland and suggested trouble with systems elsewhere in the body.

Nervousness was the most frequent symptom. This nervousness was not suggestive of the type usually met with in thyrotoxicosis.

It was in the nature of a nervous tension and sense of apprehension, associated with a feeling of carrying too heavy a load. As a rule this symptom was brought out only after careful questioning, thus differing from the objective nervousness usual in hyperthyroidism. To further illustrate this type of nervousness it may be added that several of these patients had been classified as psychoneurotics, chiefly of the neurasthenic type.

Weakness, fatigability and palpitation were common symptoms and present in nearly all of the cases. These with shortness of breath had evidently led to a previous diagnosis of cardiovascular disease in nearly a half of these patients.

Five of the 13 patients exhibited a definite hypertension, 3 showing a high diastolic pressure and cardiovascular damage. The other 2 showed definite heart and bloodvessel changes but to a lesser degree.

Attention was directed especially to the gastrointestinal tract in 3 of the patients. In one, the patient had been previously treated for over a year for gall-bladder disease and colitis; a second, diagnosed as sprue, had been treated for a chronic enteritis, for five years. The third had been under treatment for stomach trouble.

One patient had had a chronic cough and had been diagnosed as having pulmonary tuberculosis.

Among the less frequent symptoms, loss of weight was present twice; dizziness was complained of twice; tremor of the fingers but once. A feeling of warmth was not complained of in any instance in this series.

The pulse rate was usually a little increased but seldom over 80 per minute. In 2 cases the rate was between 60 and 70 per minute.

The following abstracts of case histories of a few of the patients illustrate the points we have endeavored to emphasize in this communication:

Case Abstracts. CASE I.—Mrs. A. W., aged seventy-two years, widow, complained of stomach trouble consisting of discomfort two hours after eating, gas and frequent cramps in the lower abdomen. In addition fatigability and weakness were symptoms. All of these had been present for two years. Lately the symptoms had become worse. The patient had been told she was suffering from a diseased gall bladder and colitis.

Examination showed a fairly well preserved and nourished elderly woman, Her eyes were rather bright but otherwise negative. There was a very slight enlargement of the thyroid, which was firm and apparently finely nodular. No bruit was heard. The heart was slightly enlarged and of the aortic type. The apical tones were rather loud with a soft systolic murmur and the second aortic moderately accentuated. The heart's efficiency was judged to be about 80 per cent. The aorta was moderately widened and of the arteriosclerotic type. The radial vessel walls were moderately thickened; the pulse 80 per minute and the blood pressure 150 over 70. The abdomen showed some tenderness to deep pressure in the gall-bladder region and over the sigmoid colon. There was a moderate-sized fibroid of the uterus. The reflexes were normal.

Although this patient when first examined appeared to be composed, on further observation she was found to be nervous. Her palms were always slightly warm and moist but the extended fingers showed no tremor. She gave a history of having been quite active until two years ago since when she had tired much more readily.

Our first impression caused us to accept the previous diagnosis of gall-bladder disease and colitis. Ulcer of the duodenum was also considered. In addition we made a diagnosis of arteriosclerosis of moderate grade with aortitis and myocarditis. Further a mild grade of hyperthyroidism was suspected and a basal metabolism taken which was normal. A Roentgen ray study of the gastrointestinal tract showed no organic lesion.

This patient was kept under observation for about a year and a half, during which time she showed periods of improvement. During this entire time her complaints were referable for the most part to her gastrointestinal tract. The cramps in the lower abdomen were complained of more than ever and were frequently accompanied by diarrhea. It was noted she became more nervous and tired more readily. Her pulse rate remained about the same and her basal metabolic rate rose as high as +13. During the course of treatment Lugol's solution was given, following which, for a time, her symptoms were much less but later were increased.

Finally the observable increase in nervousness, palpitation of the heart, slightly moist warm palms and the effect of iodin in addition to the complete failure of other treatment led us to suspect the small, finely nodular thyroid gland as the cause of the patient's symptoms. We hesitated to operate because of her age and lack of definiteness of demonstrable thyroid participation. Consultants blamed the cardiovascular system and colitis for the patient's condition but later felt it would be worth while to eliminate a possible thyroid element by operation as the patient was getting nowhere.

At operation the thyroid gland was found to be larger than had been previously suspected and was riddled throughout with small adenomata. The largest of these was not over 3 mm. in size. The greater part of the gland was removed.

After an uneventful convalescence all of the patient's symptoms disappeared and she has been well now for two and a half years.

Case II.—Mrs. B. P., aged thirty-six years, married, had been under the care of a doctor for some time for neurasthenia and a nervous breakdown. She complained of nervousness and tiring easily and at times of palpitation of the heart. There was no loss of weight nor any special digestive disturbance. She felt the cold keenly and complained of her hands being cold and moist. This latter she had observed especially as she was an operator in a beauty parlor.

Examination showed the patient to be nervous. She was well nourished, the skin was a little dry and the supraclavicular fat pads were noticeable. The eyes beyond being somewhat bright were negative. The neck showed a moderate diffuse enlargement of the thyroid gland, suggesting a colloid goiter. This slight enlargement had been present for fifteen years according to the patient.

The heart tones were somewhat loud at the apex and there was a soft systolic murmur not transmitted. The second aortic was of moderate intensity. The blood pressure was 140 over 70, the pulse 80 per minute when standing and 66 per minute when the patient was lying at rest. The lungs showed harsh bronchovesicular breath sounds at the left apex with a few crackles after coughing. The patient's reflexes were hyperactive, the palms slightly cool and moist. There was no tremor. The basal metabolic rate was −9. Further study of her chest showed no definite lesion and she was placed on thyroid extract 0.016 gm. once daily and a mixture containing phenobarbital and sodium iodid.

For about a month the patient stated she felt improved and the thyroid gland seemed smaller although no actual measurements were taken. The pulse rate ranged between 72 and 76 per minute standing and with the patient at rest was the same as before—66 per minute. The basal metabolism showed a rate of +1.

Following this period of improvement the patient became worse again and this encouraged us sufficiently to advise operation. The picture however was not a definite one and we operated with some trepidation. A condition of adenomatosis was found and a subtotal thyroidectomy done.

The recovery from the operation was uneventful. To our gratification and somewhat to our surprise all symptoms disappeared promptly. A year later the patient stated she had never felt better in her life. Her basal metabolism, three months after operation, was +1.

CASE III.—Mrs. C. G., married, aged forty-nine years, was sent to us with the following diagnosis: Severe hypertension, myocarditis, arteriosclerosis and nephritis. She complained of bad headaches, shortness of breath, fullness in the head and neck and fatigability. Further questioning brought out that the patient was quite nervous, complained of hot flashes and that she dated her symptoms back two years.

Our first examination supported the previously made diagnoses. She was placed on treatment including sedatives in the form of phenobarbital, ovarian injections for dysovarianism and bloodvessel spasm, heparmone for the reduction of blood pressure, digitalization and a diet.

The patient improved somewhat, the headaches becoming less pronounced, the shortness of breath somewhat less and the blood pressure lowered from 195 right, 190 left, over 100 to 175 right and left over 100. The treatment was carried out for about four months, the patient during this time being unable to do any housework and confined for the most part to bed. She still complained of marked weakness, nervousness, oppression in the head and shortness of breath.

After close scrutiny it was noticed one day that there was a slight fullness of the neck low down in front. This led to a more thorough investigation which revealed some small nodules identified as being connected with the thyroid gland. These felt about the size of the end of the small finger. Consultation with one of us confirmed this. A basal metabolism was taken and found to be +5. The patient's pulse was about 80 per minute.

Another two months intervened during which period she made little if any progress. We then explained to her the possible effect of these nodules upon her condition and advised their removal although we made it plain that we could not promise anything. On the other hand it was explained to her that no other therapeutic measures suggested themselves.

The patient proved very willing to coöperate and a subtotal thyroidectomy was performed. At operation the right lobe of the thyroid was found to be much larger than had been anticipated, the enlargement being due to the presence of several adenomata the largest of which was less than 2.5 cm. in diameter.

Convalescence was normal and the result of the operation very pleasing. About six weeks later the patient volunteered she had not felt so well for years. Her strength had markedly increased, the shortness of breath and palpitation had disappeared together with the sense of oppression and headaches. She no longer felt nervous. Three months later this patient asked us if it would be safe for her to go from house to house as a saleswoman in addition to doing her housework. At this time her blood pressure read 150 over 90. Her heart tones were of better quality, her pulse 72 per minute and the previous faint trace of albumin in the urine had disappeared.

CASE IV.—Mrs. C. J. B., married, aged twenty-eight years had been ill for four years. Tuberculosis, heart trouble and chronic sinus disease had been suspected. She had had her tonsils removed and was to have undergone a nasal operation. She complained when coming to us of weakness, fatigability, loss of weight, cough, shortness of breath, palpitation and menstrual irregularities.

Examination showed a thin, sick-looking young woman with rather high color in her cheeks. Her eyes were somewhat bright and slightly prominent, the latter being a familial characteristic. The nose showed some intranasal catarrh. The thyroid gland was slightly enlarged and smooth but firm especially on the right side.

The lungs showed harsh bronchovesicular sounds in the right upper lobe with fine râles on occasions which seemed superficial and were probably muscular. The heart was moderately enlarged, the tones loud and thumping with no murmurs. The bloodvessel walls were slightly thickened, the pressure 130 over 90, the pulse 90 per minute. There was no tremor of the fingers, the palms were cool and moist. The patient's reflexes were hyperactive. Our impressions from the examination included chronic intranasal disease, slight goiter with questionable thyrotoxicosis, questionable pulmonary tuberculosis and secondary anemia. A Roentgen ray of the chest showed nothing beyond some hilus thickening. Patient's basal metabolic rate was −13.

Treatment consisted of iron cacodylate injections, high-caloric diet and syrup of hydriodic acid, which resulted in considerable improvement. Later small amounts of thyroid extract were given as we believed the goiter was a colloid condition with hypothyroidism. The patient during this period of treatment, about two months, was being prepared for a nasal operation. She however failed to return and was not seen again for two years. At this time her complaints were largely the same as before with an added symptom of heart flutter with sudden stoppage, the history of which was characteristic of paroxysmal tachycardia. Reëxamination revealed practically the same findings as the first, the basal metabolic rate was −14. She responded unfavorably to thyroövarian extract in small amounts. On the occasion of a subsequent visit sometime after discontinuing thyroid medication this patient more forcibly impressed us as a person under a nervous strain. On examining the thyroid again we felt it was possibly the seat of an adenoma. It was explained to the patient that in spite of her low basal metabolic rate her thyroid might be the cause of her troubles and operation was advised.

At operation a smooth, rounded adenoma measuring 4.5 cm. in diameter was removed from the lower right pole. This adenoma blended with the rest of the lobe rendering its clinical recognition difficult if not impossible. The left lobe of the gland was normal.

An uneventful convalescence preceded a complete return to health and the patient has been well now for nine months.

CASE V.—Miss S. G., single, aged fifty-four years had been treated for heart trouble and tuberculosis for two years. She complained of a queer feeling in her head, cough, palpitation of the heart at times and some shortness of breath. On further questioning, she also complained of fatigability, nervousness and hot flashes.

She first consulted one of us five years ago at which time examination showed a large, well-nourished woman, somewhat nervous, with a face that flushed easily. Examination of the thyroid seemed negative. Her lungs showed wheezing throughout. Her heart was moderately enlarged, of the aortic type, with sounds which were loud and thumping. There was a soft systolic murmur at the apex and a rather loud systolic murmur at the base.

The second aortic was accentuated and ringing. The aorta was moderately widened throughout and of the arteriosclerotic type. The blood pressure was 160 over 100, the pulse 80 per minute. The vessel walls were moderately thickened. A preliminary diagnosis of arteriosclerosis, hypertension chronic, aortitis, myocarditis, bronchitis chronic, and intranasal disease was made. Patient was given a hypertension diet, syrup of hydriodic acid and phenobarbital.

She improved considerably and after a few visits was not seen again for a year when she returned complaining of cough and shortness of breath. She improved on digitalis and was seen by a throat specialist who diagnosed chronic sinusitis and advised a nasal operation. This was not done and the patient again ceased coming for a year and a half. At this time she complained of a return of all of her symptoms. In addition it was observed she was more nervous than before and that her palms were a little moist and warm. There was a slight tremor of the extended digits and she complained more of hot flashes than previously. Patient was sent to the hospital for two weeks and in the course of her examination her basal metabolic rate was determined to be −12.

She was given ovarian injections, bromide and digitalis. Later small amounts of Lugol's solution were given in spite of the low basal rate and because some of the symptoms, as in other cases, suggested over action of the thyroid. This was followed by a period of rather marked improvement, the heart palpitation disappearing and the pulse slowing to 70 per minute. Six months later the patient returned seemingly worse than ever and one day when talking to her a small lump was observed to rise from behind the left sternoclavicular region when she swallowed. This was the first intimation we had of any gross abnormality in the thyroid and we immediately followed this lead as the probable cause of at least some of her symptoms. Her basal rate was then +5.

Operation was agreed upon and a substernal adenoma 4 cm. in diameter attached to the lower left pole as well as several small adenomata of the right lobe were removed.

Two months later the patient stated she had never felt better and that a load had been taken from her head and shoulders. She was no longer nervous, showed very little shortness of breath and her cough had disappeared. Her pulse was 68 per minute, the heart tones were of much better quality and her blood pressure was 130 over 80. The tremor of the fingers and warmth of the hands had disappeared.

A great compensation to us was the feeling of gratitude and encouragement that these patients demonstrated after long periods of discouragement with their seemingly hopeless condition.

Conclusions. 1. Unrecognized thyroid adenomata as a cause of remote symptoms are frequently overlooked.

2. In patients exhibiting combinations of symptoms such as we have attempted to describe, with failure of improvement under medical treatment, adenomata of the thyroid must be carefully excluded as the underlying cause.

3. Toxic adenomata are not necessarily accompanied by an increased basal metabolic rate but may be present with a normal or subnormal rate.

4. The improvement these patients exhibit following operation is most striking and gratifying.

ANOREXIA NERVOSA, ANOREXIA, INANITION, AND LOW BASAL METABOLIC RATE.*

By John M. Berkman, M.D.,
FELLOW IN MEDICINE, THE MAYO FOUNDATION, ROCHESTER, MINN.

One hundred and seventeen cases fundamentally alike clinically and diagnosed anorexia nervosa were found in a review of the cases in which examinations had been made at The Mayo Clinic from the beginning of 1917 to the end of 1929.

The term anorexia nervosa was introduced in medical literature by Sir W. W. Gull in 1868. He presented a paper on the subject in 1873, which was published in 1888. Lasègue, in 1874, wrote a paper in which he commented on a similar condition but gave as its cause, early tuberculosis. Until 1900 the literature on anorexia nervosa consisted of reports of cases, of which there were many, comments on the disease, and criticisms. Since 1900 the reports have been contributed by Europeans, mainly the French and the Germans.

Publications on the subject in this country have been limited. Several articles have been published, however, relative to a large group of cases in which the basal metabolic rate was low, and in some cases the causal factors have been attributed to psychoneurosis and inanition.

Leede, in a publication on anorexia nervosa, considered the condition to be pluriglandular in origin, and he expressed the belief that suprarenal insufficiency plays the most important part. In his opinion, hypoglycemia is present and in his treatment of the condition he included intravenous administration of solution of glucose and injections of epinephrin. In the cases which I have reviewed, hypoglycemia has not been found.

It seems best, at this point, to give a generalized description of the appearance of these patients, their mental reactions, and the clinical history. As to their appearance, two striking characteristics attract the physician's attention at first glance: the extreme emaciation and the rather marked pallor. The pallor has led the physician to include, in recording his observations in the preliminary examination, notations referable to the presence of rather severe anemia. Questioning draws attention to certain prominent features in the mental reaction of these patients. They appear preoccupied, sit with the head bent and gaze at the floor, but when questioned, they quickly respond. However, once the question is answered, they resume the apathetic manner. They are reticent in answering questions directly concerning their mental attitude, and at times show

* Abridgement of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine, March, 1930.

negativistic tendencies. Their appearance cannot help but arouse the physician's sympathy. Two principal complaints are presented: loss of appetite, weight and strength, and various gastrointestinal disturbances, which do not correspond with the history of any of the well-known gastrointestinal diseases. On being questioned as to the cause of the anorexia, most of the patients are unable to express an opinion, or will not do so. Persistent questioning may reveal that in some cases the anorexia directly followed a psychic disturbance. In general, these patients are young; the great majority of them are girls or young women who give a history of cessation of menses of variable duration. The systolic blood pressure is low, and there is an associated slow pulse rate. Loss of weight usually is marked; loss of strength is rather slight, compared to the degree of emaciation present. Complete laboratory examinations give practically negative results. A depressed basal metabolic rate is consistently present. Frequently hypoacidity of the stomach is present, and more frequently, a high total gastric content, denoting lessened gastric motility.

In the group of cases reported I have not considered those patients aged less than thirteen years, observed in the section on pediatrics, nor the group of less than 10 cases in which diagnosis of anorexia nervosa was made prior to 1917.

H. S. Plummer, in 1917, began the investigation of this group in The Mayo Clinic, and in many cases, various studies of metabolism and of chemical changes in the blood were conducted. Since 1917, cases of anorexia nervosa have been studied exhaustively whenever possible, and nothing which would satisfactorily explain the symptoms or physical condition of these patients has been found.

Although anorexia nervosa does not limit itself to the poor, and there is nothing to substantiate the idea that poverty is a factor in the etiology of the disease, the great majority of the cases were among persons whose financial circumstances were not the best. Therefore both treatment and study of the condition have been more or less difficult.

In The Mayo Clinic, during the years reviewed in connection with this article, the diagnosis of anorexia nervosa occurred as follows: 1917, one case; 1918, no cases; 1919, one case; 1920, 4 cases; 1921, 4 cases; 1922, 16 cases; 1923, 7 cases; 1924, 8 cases; 1925, 14 cases; 1926, 16 cases; 1927, 15 cases; 1928, 13 cases, and 1929, 18 cases.

A review of 117 cases might lead one to believe that the occurrence of anorexia nervosa is not at all infrequent; however, considering the yearly registration of patients at The Mayo Clinic, and the fact that this total of 117 cases extends over a period of thirteen years, it is easily seen that the disease is fairly infrequent. Eighty-nine patients in the group studied were females and 28 were males. The ages of the female patients were as follows: 1 patient was aged thirteen years, 11 were aged fourteen and fifteen, 57 were between

the ages of fifteen and twenty-nine, 16 were between thirty and forty, and 4 were aged forty years, or more. The ages of the male patients were: 17 between fifteen and twenty-nine years, 9 between thirty and forty, and 2 were aged forty years, or more.

Eighty-five of the 89 female patients were well within the normal menstrual age limits, and of these, 45, approximately 53 per cent, had amenorrhea. Four patients had passed through the menopause, and in 2 of these the menopause had been artificially established.

Several studies of basal metabolism were made in each case; in view of the element of nervousness or fear of the apparatus, which frequently is responsible for elevated rates, the lower of the first two rates obtained was chosen. These values are shown in Table I. One of the patients, a woman, had been examined prior to coming

TABLE I.—METABOLIC RATE IN CASES OF ANOREXIA NERVOSA.

Males.	Females.	Range of basal metabolic rate.
1	12	0 to −10
6	28	−10 to −20
10	36	−20 to −30
10	11	−30 to −40
1	1	−40 to −42

to the Clinic, and her basal metabolic rate had been well below normal. She had been given a thyroid preparation for seven weeks previous to her examination in the Clinic. At the time of examination here the basal metabolic rate was +1. This case was the only one of the group in which the basal metabolic rate was not below zero. Curschmann, in a review of cases in which the basal metabolic rates varied from normal, concluded that psychoneurosis plays an important part in the depression or elevation of the basal metabolic rate. The depression in metabolism in the cases reported herein had no consistent relationship to the severity of the gastrointestinal symptoms, dryness of the skin and hair, loss of weight or strength, the systolic blood pressure, or the degree of anorexia. Many patients with extreme emaciation, and who were severely ill, however, had basal metabolic rates considerably below normal. Some patients had low basal metabolic rates and complained considerably of gastrointestinal symptoms, but they were not severely ill and the emaciation was not so great as in the cases in which the metabolic rates were higher.

In 47 cases, 40 per cent of the entire group, neurologic and psychiatric examinations were made, to insure against the possible presence of psychosis or of an intracranial lesion. Roentgenograms of the head were taken in many of these cases, but in none was pathologic change evident; the sella turcica was normal in all. As ophthalmologic examinations of the fundus are prerequisites to neurologic examinations in the Clinic, it would seem that gross lesions of the pituitary gland and of structures in its immediate vicinity were

fairly well ruled out. A definite psychologic basis for the anorexia was brought out in only 20 cases. A more exhaustive investigation probably would have disclosed a psychologic basis for the anorexia in many more cases, but in this respect there were two principal difficulties: (1) The diagnosis of anorexia nervosa was not suspected until after the history was recorded in most of the cases, and in many, not until the examination had been completed. (2) The reticence of many of these patients probably would have defeated every effort to elicit a psychologic basis for the anorexia.

In 51 cases, 43 per cent of the entire group studied, dryness of the skin and hair was noted; the condition was present in 39, 43 per cent of the female patients, and in 12, 47 per cent of the male patients.

Gradation of the anorexia present in these cases has been made (Table II), to give the reader some idea of the loss of appetite which occurred. Grade 1 represents moderate but definite anorexia; Grade 4 indicates complete loss of appetite. In many of the latter group of cases it was necessary to institute tubal feeding.

TABLE II.—LOSS OF APPETITE, WEIGHT AND STRENGTH IN ANOREXIA NERVOSA.

Males.	Females.	Quantitative expression of loss of	
	2	Appetite*	1
10	12		2
4	26		3
14	49		4
	1	Weight†	Questionable
	3		0
1	6		1 to 10
3	16		10 to 20
10	24		20 to 30
5	18		30 to 40
5	9		40 to 50
1	5		50 to 60
1	2		60 to 70
	2		70 to 80
2	3		90 to 100
	11	Strength*	0
5	30		1
17	33		2
5	12		3
1	3		4

* Grade. † Pounds.

Gradation of loss of weight also is shown in Table II. In the 2 cases in males indicated as being within the range of 90 to 100 pounds, 1 patient lost 98 pounds and the other 105 pounds. In the 3 cases in females, the loss of weight was, respectively: 98 pounds, 100 pounds, and 101 pounds.

I have also attempted (Table II) to grade the loss of strength. Grade 1 represents a loss of strength apparent to the examining

physician. Patients whose loss of strength was graded 4 were unable to bear their own weight.

TABLE III.—SYSTOLIC BLOOD PRESSURE.

Range, millimeters of mercury.	Cases.
65 to 70	1
70 to 75	3
75 to 80	9
80 to 85	8
85 to 90	22
90 to 95	18
95 to 100	20
100 to 105	10
105 to 110	11
110 to 115	5
115 to 120	7

The systolic blood pressures in this group of patients are given in Table III. The determinations were made during rest, at the time of the metabolic test.

Two cases were not recorded in Table III; in one the readings were 130 systolic and 76 diastolic, and in the other, 140 systolic and 92 diastolic. Although the systolic blood pressure was not consistently low, it can at least be said that the general trend of this group is toward arterial hypotension.

Lusk presented, in chart form, observations on the systolic blood pressure of a man who underwent voluntary starvation over a period of thirty-one days. At the beginning of the fast the systolic blood pressure was found to be at 132 mm. of mercury. During the fast, the systolic blood pressure became gradually depressed, until at the end of the thirty-one days the reading was found to be 100 mm. of mercury.

In relation to the depression of the systolic blood pressure, it might be worth while briefly to review the following case:

CASE I.—A girl, aged fifteen years, presented herself at the Clinic with a complaint of difficulty in swallowing; this trouble had been of short duration. A diagnosis of hysterical dysphagia was made and esophageal bougies were passed. At this time, her weight was 115 pounds, which was her usual weight, and her blood pressure was 118 systolic and 90 diastolic. Eight months later she returned for further examination. She had lost 26 pounds, amenorrhea had been present for four months and the basal metabolic rate was −30. She complained of vague abdominal discomfort, severe constipation, and mild dysphagia. A diagnosis of anorexia nervosa was made. At the time of this visit to the Clinic her blood pressure was 90 systolic and 60 diastolic. These readings of systolic blood pressure were both determined in the examining room.

So far as had been determined, the pulse pressure and respiratory rate were of no significance. Lusk referred to the fact that in voluntary starvers the temperature does not vary from normal. In the group of cases reviewed in the Clinic, the readings of temperature

correspond to those which would be found in the same number of normal persons.

The pulse rate for each minute, determined at the time of the metabolic tests, was 30 to 40 in 2 cases; 40 to 50 in 22 cases; 50 to 60 in 38 cases; 60 to 70 in 20 cases; 70 to 80 in 22 cases; 80 to 90 in 9 cases, and 90 to 100 in 3 cases. Although there was no consistence, there seems, on the whole, to have been a tendency toward a subnormal pulse rate in the group.

In 12 cases, generalized diseases of the skin were found, and in 12 cases there was brownish discoloration of the skin of the abdomen. In only 3 cases were there both disease of the skin and brownish pigmentation.

In the entire group of 117 cases reviewed, there were but 4 in which the patient did not complain of gastrointestinal disturbances. In 32 cases there was one of an association of several of the following symptoms: distress, gas, nausea, or a sensation of abdominal heaviness, fullness or pressure. One patient had some of the symptoms just named and diarrhea. There was pain with some of the stated symptoms in 12 cases; pain alone in 2 cases; pain with vomiting in 24 cases; pain with vomiting and diarrhea in 5 cases; vomiting and diarrhea in 3 cases, and vomiting alone in 34 cases.

It will be seen, from the foregoing list, that vomiting occurred in 66 cases, 56 per cent of the cases in the entire group. With one exception, the gastrointestinal symptoms were aggravated immediately after ingestion of food. The one exception was the instance of a man who had an associated duodenal ulcer. He had the characteristic symptoms of duodenal ulcer three to four hours after meals, but the vomiting which occurred immediately after he took even small amounts of food was much more distressing to him than his symptoms of ulcer.

In most cases, pain was referred to the epigastrium; however, there were several patients who complained of pain in the lower right quadrant of the abdomen. Several of these patients had undergone appendectomy without obtaining relief. None of the remainder of the group was thought to be suffering from appendicitis. Whenever there was a complaint of diarrhea, examinations of stool and proctoscopic examination were made, as well as roentgenograms of the colon. In many instances constipation to the point of obstipation was a frequent complaint. In the examinations of several of the older patients, roentgenograms of the colon were made in order to exclude the possibility of neoplasm.

Roentgenograms of the stomach were made in 93 cases and analysis of the gastric content in 92. Of the former, 91 cases were reported negative by the roentgenologist; in the other 2, the diagnosis was duodenal ulcer and indeterminate obstruction at the pylorus, respectively. These 2 patients subsequently came to operation. The results of the analyses of gastric content are reported in the

usual way; that is, free hydrochloric acid of 20 would indicate that 10 cc. of filtered gastric content were neutralized by 2 cc. of $\frac{N}{10}$ sodium hydroxid. Free hydrochloric acid was not found in 11 cases; hydrochloric acid was well below 20 in 22 cases and well above 40 in 7 cases. Acidity was normal in 52 cases. In the Clinic, the normal range of free hydrochloric acid is considered to be from 20 to 40.

Although there is nothing consistent in regard to the absence or presence of free hydrochloric acid in these cases, there is a tendency to hypoacidity. Surmount, in an article in which he classified and commented on different types of anorexia, stated that he had found a condition of achlorhydria present in the type of person that is subject to anorexia nervosa. Of the 9 cases of diarrhea, there was associated achlorhydria in 3; the gastric content in the other 6 was well within normal limits of acidity. Examinations of stool were uniformly negative.

Associated diseases were found in the group. Raynaud's disease was present in one case. Addison's disease was suspected, but not proved in 3 cases; one of the patients is dead. Pellagra was found in one and tetany in 2 cases. In 3 cases there was associated pitting edema of the lower extremities.

Thyroidectomy had been previously performed in 2 cases, in one case for simple adenoma and in the other for exophthalmic goiter; in both instances anorexia nervosa developed one year later. Some form of surgical treatment was carried out in 7 cases: in one case, amputation of the breast was performed for carcinoma; in 2 cases, gastroenterostomy was necessary for duodenal ulcer and contracted pyloric ring, respectively; the latter has been referred to as a case of pyloric obstruction. In the 4 remaining cases the operations were minor; that is, dental extraction, making of a window in the maxillary antrum and tonsillectomy.

An attempt was made to cause elevation of the metabolic rate in 85 patients, 73 per cent of the total number included in this study. Sixty-three patients were given desiccated thyroid gland alone, 14 received both desiccated thyroid gland and thyroxin, and 8 were treated with thyroxin, alone. For various reasons no attempt was made to cause elevation of the metabolic rate of the remaining 22 patients: the financial circumstances of some were such as to prevent them from remaining long enough for establishment of dosage; in some the rate was not low enough to warrant the administration of a preparation of thyroid gland; some patients themselves did not consider it worth while to remain for treatment on being informed that cure could not be promised. One patient was given insulin as adjunctive treatment; five units were administered three times daily for several days. There seemed to be some improvement in the patient's appetite, but the treatment was discontinued for lack of definite evidence of value.

Of the group just enumerated, in which treatment with a preparation of thyroid gland was undertaken, 36 patients remained long enough to allow the dosage to be established, and 49 were hospitalized for periods of from ten days to two months.

Two phases of the treatment of anorexia nervosa through the administration of thyroid products are of prime importance: (1) the establishment of the individual dose; (2) the administration of adequate nourishment. The extent to which the metabolic rate may be elevated depends on the amount of nourishment the patient will take; that is to say, if the metabolic rate is elevated and the intake of food is not increased, there will be loss of weight. This is to be guarded against, in view of the fact that when the patient's condition has been such as to necessitate hospitalization, considerable loss of weight has already occurred. It is important that these patients receive the minimal degree of sympathy, but it is of equal importance that they be not antagonized. The problem of nourishment in these cases is difficult enough in the presence of a high degree of empathy between the physician and patient but becomes almost insurmountable in the face of complete lack of the patient's coöperation. Many of these patients may be encouraged to take food in increasing calorie value; others will take only small amounts of food, or none at all, and in this group it may be necessary to pass a stomach tube and keep it in place for some time. Feedings through the tube may be given at frequent intervals, but the intake of food should be increased gradually, for the gastrointestinal symptoms occasionally are exaggerated when the increase is too rapid. Often, following removal of the tube, the patient will be willing to eat; in other cases it may be necessary to replace the tube. The problem of nourishment persists throughout the entire course of treatment and cannot be overestimated.

Lévi reported a few cases of anorexia, emaciation, and low basal metabolic rate, in which the patients were benefited by treatment with thyroid extract. He attributed the condition to thyroid deficiency, but in the group of similar cases herein reported, hypothyroidism has not been considered a causative factor. Bauer, in considering disorders of metabolism due to neurotic conditions, mentioned one case of neurosis with a metabolic rate of −18, in which very good results were obtained by treating the patient with thyroxin and thyroid extract. Faber, in a publication on anorexia nervosa, reported cure in several cases in which the only treatment was increased intake of food. The basal metabolic rates were not mentioned and evidently treatment with preparations of thyroid gland was not given.

In some of the hospitalized patients, it was possible to cause elevation of the metabolic rate to normal; in some, general improvement in appetite and mental attitude at the time of dismissal was noted. It might be said, here, that the favorable results which we

have seen have not occurred in a short period of time, but over a period of several months and even of several years.

The patients who were treated did not respond uniformly to treatment with preparations of thyroid gland. The rate was elevated to a certain extent in some cases, but it was impossible to cause elevation of the rate to normal on account of complaints of tachycardia, a sense of cardiac oppression, palpitation, headache and generalized aching. In other instances in which the patient responded slowly to administration of thyroid extract, thyroxin was used intravenously for a few doses, after which thyroid extract or thyroxin was given by mouth.

In each of the groups of 85 patients who were given a preparation of thyroid gland to cause elevation of the metabolic rate, the patient was given the individually established dosage and the drug was then continued under the observation of the home physician. The patient was instructed regarding the symptoms which might occur in the event of overdosage, that is, generalized aching, headache, palpitation, tachycardia, loss of weight, and increased nervousness.

Some of the patients returned to the Clinic for observation later, and it was found that the results of treatment with a preparation of thyroid gland were, in general, favorable. There was one group of patients, however, in which the basal metabolic rate was about the same as it had been when the patients were first examined at the Clinic. It is possible that the absence of any increase in metabolic rate could be explained on the basis of a decrease in the intake of food after the patient had returned home, or failure of absorption of the thyroid extract in the gastrointestinal tract. In another group, just the opposite occurred. The basal metabolic rate had increased to above +15; in one case it reached +30. After these patients had returned home, the appetite and intake of food had markedly increased. In spite of this, these patients had continued the treatment with a preparation of thyroid gland in the dosage which had been determined on at the time of their anorexia and low intake of food. Their return to the Clinic was occasioned by gradual loss in weight, mild tachycardia, and a sensation of all not being well with them. On the whole, these patients appeared to be considerably improved.

It can be said that both the mental and physical improvement is appreciable and in some cases marked, when the metabolism can be maintained near normal without loss of weight. It has been observed that early recognition and treatment of the disease results in a greater degree of improvement over a shorter period of time than is true in cases in which the condition is of long-standing.

In 68 of the 85 cases in which the patient was dismissed with directions to take a preparation of thyroid gland, the subsequent course is known. In 17 cases further information is not obtainable at present. Of the 68 patients whose progress could be followed, 6

apparently returned to normal condition, 24 were markedly improved and 12 received definite benefit. Of the remaining 26, treatment did not effect a change in 14, and 12, 9 of whom are now dead, grew progressively worse. Information is not available relative to 8 of those who are dead. One patient died while in the care of the Clinic; in this case it had been impossible to maintain elevation in metabolic rate although the basal metabolic rate had been raised for a day or so at a time. Death occurred after a period of hospitalization of six weeks. The postmortem examination gave essentially negative results except for the discovery of evidence of bronchial pneumonia.

It must be borne in mind that these data include those relative to patients seen in the Clinic within the last year, and also in part they have been obtained from records of several years ago. In all probability, more exhaustive investigation for information in these cases will reveal additional deaths, and likewise, subsequent data may show the results to be more favorable.

I already have stated that the patients had marked pallor, suggestive of anemia. The records show, however, that the erythrocyte count was well above 4,000,000 per c.mm. in all but five instances; in these five, the lowest erythrocyte count was above 3,700,000.

The mental reaction was not constant. Some patients were definitely psychoneurotic and apprehensive. In a larger group, which included the more advanced cases, the mental reactions were quite similar; these patients were apathetic, reticent, and some showed negativistic tendencies. It is probable that the mental reaction represents an exaggeration of intrinsic traits. In 20 of the cases studied, the onset of anorexia apparently could be traced back to a psychic disturbance. Psychic disturbance may occur in mentally normal persons, or it may be superimposed on mental make-up often described as social inadequacy or biologic inferiority. To substantiate the statement that anorexia nervosa may occur in mentally normal persons, the following case is reported:

CASE II.—A man, aged nineteen years, first came to the Clinic in November, 1920. Eleven months previously he had undergone appendectomy because of an indefinite complaint of pain in the lower right quadrant. The principal complaint at the time of examination at the Clinic was pain in the lower right quadrant and constipation. He stated that four years previously, for a period of two months, he had had attacks occurring every week or ten days, lasting from a few moments to an hour, consisting of right abdominal pain, nausea, and occasional vomiting followed by vertigo, which lasted about one day. He had had four or five of these attacks. Subsequent to this, he began to have constant belching, coming on after eating and occasionally without eating. The constipation grew progressively worse. The appetite became very poor. Two years previous to his examination at the Clinic he noticed that if he would eat more than a certain amount a dull, heavy, epigastric sensation would develop, accompanied by general sensations of languor, and palpitation. The intake of food, therefore, became insufficient to maintain his weight.

Examination revealed an extremely emaciated man. The skin was harsh and dry. He weighed 82 pounds, which was 25 pounds less than his normal weight. The blood pressures were 88 systolic and 62 diastolic, and the pulse rate was 44. The physical features otherwise were negative. Repeatedly, specimens of urine were normal. A complete examination of blood was done; erythrocytes numbered 4,160,000 per c.mm.; the concentration of hemoglobin was 72 per cent; the Wassermann reaction was negative. Analysis of gastric content disclosed total acidity of 60 and free hydrochloric acid of 44, with a total quantity of 75 cc. recovered. Roentgenograms of the head, thorax, stomach and colon gave negative results. Electrocardiograms gave evidence of sinus bradycardia, and the basal metabolic rate was −40. The treatment with a preparation of thyroid gland was instituted, and the intake of food was increased. This patient remained under observation from December 1, 1920, until January 27, 1921, when he was dismissed to continue treatment with a preparation of thyroid gland at home. The basal metabolic rate was +1. There seemed to be slight improvement in his condition.

June 16, 1921, the patient returned to the Clinic. The basal metabolic rate was +16. Decided improvement was apparent in the patient's condition; his appetite was good, there was improvement in his facial expression and mental attitude and his only complaint was occasional slight pain in the region of the umbilicus. In spite of the elevated metabolism, the patient had gained 12 pounds. He returned home and discontinued the thyroid treatment.

September 17, 1921, the patient again returned to the Clinic. The basal metabolic rate was −15. He had gained 15 pounds. He felt fairly well and noticed more improvement in his appetite. He was troubled with a buzzing sound in his ears and a slow pulse, with a sensation of tiredness and drowsiness. His general strength was greatly improved. Treatment with a preparation of thyroid gland was reinstated, and in seven days the basal metabolic rate had been elevated to +2. He returned home, again taking a preparation of thyroid gland. In May, 1922, he again consulted the Clinic, in perfect health. His basal metabolic rate was −4. He was eating well, had no abdominal symptoms, and his nutrition was good. His mental attitude was normal.

Subsequently this patient attended college, and in January, 1927, a letter was received from one of his professors, part of which read, "He has majored with me in zoölogy and I considered him probably the most persistent, capable and enthusiastic student I have ever had. He does high-grade work, not only with me, but in all of his subjects. Recently he was elected to membership in the Phi Beta Kappa fraternity."

Lusk, observing professional starvers, stated that one cannot trace the cause of lowered metabolism in cases of undernutrition to reduction of the mass of body protein, nor to reduction in the mass of body substance itself. It exists in an innate protective mechanism the nature of which one can only dimly surmise. The young men, so nourished, lacked physical strength and lacked a sense of well-being. Also, Lusk said; "Voluntary starvation shows a loss of buoyancy of spirit, a decreased desire to work and a decrease in the actual power of working."

In professional starvers, it was noted that the metabolism did not return to normal soon after ingestion of food. Lusk stated: "The nutritive condition of the body and not the influx of food on the

day previous, determines the height of the metabolism." It has been said in the foregoing paragraphs that the favorable results of treatment did not occur immediately but after several months or longer, in some cases.

The results of postmortem examination in the one case of death that occurred while the patient was under the care of physicians of the Clinic were entirely negative, with the exception of disclosing evidence of bronchial pneumonia, which had been present only two days prior to death. Marshall and Stephens each reported negative results of postmortem examination in cases of anorexia nervosa. Voit, after his experiments in starvation, concluded "Death from starvation is primarily due to loss of substance in organs important to life, but it may also ensue under certain circumstances as a result of deficient nutrition to these organs."

In 7 patients in whom no psychologic basis for the anorexia was brought out, associated conditions were found. One patient suffered from narcolepsy and 6 from encephalitis; 2 of the latter exhibited definite symptoms of Parkinson's disease. One of the patients with Parkinson's disease did not show signs or symptoms of the condition at the time of his first visit to the Clinic, when a diagnosis of anorexia nervosa was made. The patient returned fourteen months later, presenting a typical Parkinsonian syndrome. Since we are just beginning to recognize the various late effects of encephalitis, it is possible that encephalitis may be later shown to have been an important factor in causing the anorexia in some cases of so-called anorexia nervosa.

Assuming that all possible lesions of the thorax and gastrointestinal tract are excluded, the most important conditions to be considered in a differential diagnosis are myxedema, thyroiditis, intracranial lesions, and mental disorders. It is common knowledge that the insane may go on a hunger strike at any time. This fact makes important the exclusion in severe cases of anorexia nervosa of the presence of mental disorders, especially of compulsion-obsessions and psychosis of a depressive nature.

The sequence of events appears to be as follows: A psychic disturbance develops in a number of persons which is directly responsible for, and followed by, loss of appetite. The resulting lessened intake of food finally leads to inanition, which is associated with a process of bringing about a low rate of metabolism. A person with a low metabolic rate requires less nourishment than one with a high rate of metabolism, and in this manner a condition which simulates a vicious circle is brought about. These patients, in the first part of the course of the disease, lose most of their weight. At a certain point the weight becomes more or less stationary. It appears that the depression of the basal metabolic rate acts as somewhat of a protective mechanism, for if the metabolism remained normal, these patients eventually would go on to death, which would occur

much earlier than it actually has occurred in any case. In severe cases of long-standing the least improvement is seen. The fact that the favorable results which we have observed have occurred after considerable time, even though the metabolism and intake of food had been maintained near normal, suggests that other secondary degenerative processes have occurred as a result of the inanition.

In cases of low basal metabolic rate due to hypothyroidism, the clinical picture follows the occurrence of low metabolism. In such cases, although there is some loss of appetite and a decreased requirement for nourishment, the weight is maintained or even increased, as in cases of myxedema. In anorexia nervosa it seems that the opposite occurs; that is, the low basal metabolism follows, rather than precedes, the clinical picture. Although these patients with anorexia nervosa were to some degree intolerant to cold, and a few of them had dry hair and skin, they did not give evidence of symptoms of myxedema, although many of them had metabolic rates much lower than rates frequently found in marked cases of myxedema. In cases of hypothyroidism in which the basal metabolic rate is lower than −20 there is facial edema. This has not been true in any of the cases which were reported as anorexia nervosa, and I have not considered these cases to be hypothyroid states.

I believe that there are other cases of low basal metabolic rate without anorexia which are due to inanition. The number of cases probably is not large. I have recently seen one patient with low rates, who has been eating very little over a period of two years. Two years ago all of his teeth had been extracted, and since that time he has been unable to obtain satisfactory artificial dentures. His complaints were similar to those of cases presented in this paper; namely, mild diarrhea, feeling of fullness and distress, and a dull aching pain in the epigastrium. Complete examination did not reveal organic abnormality except loss of weight. The basal metabolic rate was −29.

Conclusions. 1. Anorexia nervosa may be said to constitute a definite clinical entity. Briefly, its clinical characteristics are anorexia, inanition, emaciation, various gastrointestinal disturbances, marked nervous manifestations, and low basal metabolic rate. In our experience the condition is not as common as one would expect; 117 cases were so diagnosed in this Clinic in thirteen years.

2. It seems probable that the low basal metabolic rate is the result of inanition.

3. The absence of any demonstrable pathologic change characterizes the condition as a physiologic disorder secondary to a psychic disturbance.

4. The reëstablishment of normal intake of calories is the direct goal, and to this end treatment with a preparation of thyroid gland has been proved to be a valuable adjunctive measure.

5. A similar condition due to inanition may be found in some cases in the absence of anorexia.

BIBLIOGRAPHY.

1. Bauer, Julius: Irreführende Gaswechselbefunde, Klin. Wchnschr., 1928, **7**, 2090.
2. Curschmann, Hans: Die Stoffwechseluntersuchung in der Diagnostik der Neurosen, Deutsch. med. Wchnschr., 1926, **52**, 9.
3. Faber, Knud: Anorexia Nervosa, Arch. f. Verdauungskr., 1926, **37**, 17.
4. Gull, W. W.: Anorexia Nervosa (Apepsia Hysterica, Anorexia Hysterica), Trans. Clin. Soc. London, 1888, **7**, 22.
5. Lasègue, C.: De l'anorexie hystérique, Arch. gén. de méd., 1873, **131**, 385.
6. Leede, C. S.: Anorexia Nervosa: Hypoglycemia or Hypoadrenia, Northwest Med., 1928, **27**, 233.
7. Lévi, Léopold: Anorexie mentale et corps thyroide, Encéphalé, October, 1922, p. 507.
8. Lusk, Graham: The Elements of the Science of Nutrition, Philadelphia, W. B. Saunders Company, 4th ed., 1928, p. 764.
9. Marshall, C. F.: A Fatal Case of Anorexia Nervosa, Lancet, 1895, i, 149.
10. Stephens, Lockhart: Case of Anorexia Nervosa: Necropsy, Lancet, 1895, i, 31.
11. Surmont, H.: Les diverses formes de l'anorexie nerveuse leur diagnostic, Médecine, 1920, **1**, 603.
12. Voit, E.: Quoted by Lusk.

REVIEWS.

REFLEX ACTION: A STUDY IN THE HISTORY OF PHYSIOLOGICAL PSYCHOLOGY. By FRANKLIN FEARING, PH.D. Pp. 350; 12 illustrations. Baltimore: The Williams & Wilkins Company, 1930. Price, $6.50.

IT may be regretted that the following sentence does not appear upon the first page instead of near the last.

"From the point of view of physiological psychology we are concerned with the reflex act as a part of the total response pattern of the functioning organism, rather than with the analysis of the functional components of the isolated reflex arc."

To those whose interest in the subject is thus limited, the book gives a perspective of the development of certain trends in psychology arising from the early work on reflexes and a consideration of some recent applications of reflex studies on man to problems in that field. On the other hand, those who look to the analysis of the functional components of reflex arcs for clews to the complex situations which confront the psychologist probably will be disappointed by the author's treatment of his theme. Unfortunately Chapters X and XI are mangled by omission of many pages and misplacement of others, at least in the copy furnished for review.

G. McC.

INFANT NUTRITION. By WILLIAMS MCKIM MARRIOTT, B.S., M.D. Pp. 375; 53 illustrations. St. Louis: C. V. Mosby Company, 1930. Price, $5.50.

FROM the pen of one whose studies in the laboratory and clinical fields of infant feeding have done much to further that branch of pediatrics, this book has been long expected and awaited.

The first part of the book deals with growth, development, the energy requirements of infants and the metabolism of the food elements, salts and vitamins. This section is handled in a simple, but complete manner, omitting nothing, but avoiding controversial matter. Following this, digestion is discussed and a special chapter is devoted to the stools in infancy and their significance.

One large chapter is devoted to breast feeding and then the subject of artificial feeding of the normal child is considered. The

various types of feeding are discussed and the advantages and disadvantages of each are presented in such a fashion that the particular indications for that food are made very clear.

The various disorders of nutrition such as malnutrition, marasmus, diarrhea, dysentery, celiac disease, vomiting, pyloric stenosis and constipation are fully considered. They are discussed in the light of the newer advances in nutritional physiology. There are complete but not exhaustive chapters on prematurity, rickets, tetany and scurvy.

Two chapters in the book are outstanding. The first is an exposition of the relationship between the common infections of infants and nutritional disease. Much more space is devoted to this important phase of infant feeding than in most other books of this class. The author's pioneer opinions, daily becoming better accepted, are here very clearly stated, especially in the matter of mastoiditis. The other outstanding chapter is on anhydremia, acidosis and alkalosis in which Dr. Alexis F. Hartmann is collaborator.

The book closes with a chapter on pediatric technique, which omits the more obvious procedures, and clearly describes the more difficult ones. Treatment is in many instances explained by illustrative cases, confusing alternatives being avoided, but the reason for each procedure being definitely stated. The Reviewer finds little to criticize about the book; he is a little disappointed that more space is not allotted to the nutrition of the second year and to the subject of anorexia.

Dr. Marriott is to be congratulated upon his simple grammatical construction and lively style which sustains the attention and makes the book easy to read. These virtues are enhanced by its being printed on an unglazed paper in rather large, clear type.

For its crystallization of opinion this book will recommend itself to the pediatrist. As a text it will be found thorough and up to date and will be invaluable to the student and practitioner of medicine. The Reviewer feels that it is one of the most important books in its field. J. S.

ANATOMISCHE ORGANKRANKHEITEN AUS SEELISCHER URSACHE. By LEOPOLD ALKAN, M.D. Pp. 142. Stuttgart and Leipzig: Hippokrates-Verlag, 1930. Price (unbound), R.M. 9.

THIS volume, which is the fourth of a series intended to present the fruits of clinical research for the benefit of the specialist and the general practitioner, is typographically very attractive; it is printed in heavy-faced Latin characters on excellent paper, opaque and without luster. The latter characteristic is one which American medical publishers might well imitate.

The title may be translated: Organic Visceral Diseases of Psychic Origin. The author adopts the modern dynamic psychology, and on this basis divides the neuroses and the psychoneuroses into transference and narcissistic neuroses. He emphasizes the idea that the mind, or soul, is a function of the whole body (*cf.*, the "heart," "veins" and "bowels" of the Bible), rather than of the brain alone. He believes that there is no sharp line between the functional and the organic, and that visceral neuroses, affecting as they do, the vegetative system, are the precursors of organic changes in the organs. Conversely organic diseases are invariably accompanied by functional and psychic disturbances. Therapy must, therefore, invariably be aimed in three directions, namely: "(1) In the direction of the psyche; (2) in the direction of the vegetative, that is, the sympathetic, parasympathetic and endocrine systems; (3) in the direction of the involved organs." He emphasizes the importance of psychic factors even in conditions usually considered purely organic. In connection with treatment, he alludes to psychoanalysis, but apparently in practice uses the point of view rather than the method. On the basis of these ideas, and with emphasis on the approach from the three angles mentioned, he elaborates the treatment of various circulatory and gastrointestinal neuroses and of their direct physiologic effects and secondary anatomical sequelæ. This book is of special interest at this time because of the present tendency to consider the psychiatric point of view in the diagnosis and treatment not only of neuroses, but also of medical diseases in general. C. F.

BOOKS RECEIVED.

NEW BOOKS.

The Medical Clinics of North America, Vol. 14, No. 1, University of California Number, July, 1930. Pp. 278; 54 illustrations. Philadelphia: W. B. Saunders Company, 1930.

*Clio Medica, Vol. I, The Beginnings—Egypt and Assyria.** By WARREN B. DAWSON, F.R.S.E. Pp. 86. New York: Paul B. Hoeber, Inc., 1930. Price, $1.50.

*Clio Medica, Vol. II, Medicine in the British Isles.** By SIR D'ARCY POWER, K.B.E., F.R.C.S. (ENG.). Pp. 84; 1 illustration. New York: Paul B. Hoeber, Inc., 1930. Price, $1.50.

*Clio Medica, Vol. III, Anatomy.** By GEORGE W. CORNER, M.D. Pp. 82; 8 illustrations. New York: Paul B. Hoeber, Inc., 1930. Price, $1.50.

* Reviews of titles followed by an asterisk will appear in a later number.

*Hypertension.** By LESLIE T. GAGER, M.D. Pp. 158. Baltimore: Williams & Wilkins Company, 1930. Price, $3.00.

*Annals of Roentgenology, Vol. XI, The Chest.** By L. R. SANTE, M.D., F.A.C.P., F.A.C.R. Edited by JAMES T. CASE, M.D. Pp. 561; 246 illustrations. New York: Paul B. Hoeber, Inc., 1930. Price, $20.00.

Report of the Fifth International Congress of Military Medicine and Pharmacy, London, May, 1929, By COMMANDER WILLIAM SEAMAN BAINBRIDGE, M.C.-F., U. S. N. R. Pp. 154; 25 illustrations. Menasha, Wis.: George Banta Publishing Company, 1930.

*Affections of the Eye in General Practice.** By R. LINDSAY REA, B.Sc., M.D., M.Ch., F.R.C.S. Pp. 155; 40 illustrations. Philadelphia: Lea & Febiger, Inc., 1930. Price, $3.50.

NEW EDITIONS.

The Action of Muscles. By SIR COLIN MACKENZIE, M.D., F.R.C.S., F.R.S. (EDIN.). Pp. 288; 100 illustrations. Second edition. New York: Paul B. Hoeber, Inc., 1930. Price, $3.50.

The book deals clearly, if dogmatically, with the aspects of the subject essential to orthopedics. It includes interesting deductions from comparative anatomy. It lays just emphasis upon reciprocal innervation. In the application of this principle to muscles passing over two joints, however, conclusions are drawn with which the Reviewer cannot concur.

A Textbook for Midwives. By JOHN S. FAIRBAIRN, M.A., B.M., B.CH. (OXON.), F.R.C.P. (LOND.), F.R.C.S. (ENG.), MAST. MIDW. SOC. APOTH. (LOND.). Pp. 369; 119 illustrations. Fifth edition. New York: Oxford University Press, 1930. Price, $8.00.

This quite comprehensive and up-to-date treatise on obstetrics is intended not alone for pupil midwives of England but for their teachers, medical missionary workers and nurses in Colonial services. The whole subject of obstetrics, normal and abnormal, including operations, and such allied subjects as cancer of the uterus and venereal diseases are covered in such detail as to make an American physician wonder at the mental appetite and digestion of an English midwife. But, as the author remarks, a new type of obstetrician, an educated midwife, is under development, and it is for her that the book is intended. In that case one notes a paucity of illustrations of the more practical procedures she might need to undertake.

Clinical Features of Heart Disease. By LEROY CRUMMER, M.D. Pp. 415. Second edition. New York: Paul B. Hoeber, Inc., 1930. Price, $4.00.

The author has undoubtedly been a conscientious student of the clinical features of heart disease. His style is clear so that the book is easy to read. Unfortunately, however, it contains so many statements at variance from the views of competent investigators of heart disease that one hesitates to recommend it. In this respect the present edition is not much of an improvement over the first.

Physical Diagnosis. By RICHARD C. CABOT, M.D. Pp. 529; 280 illustrations. Tenth edition. New York: William Wood & Co., 1930.

This well-known book on diagnostic methods and processes is recommended without reservation to practitioners of medicine. One can scarcely fail to benefit greatly from its study. Very little new matter has been added so that those who possess the ninth edition will not need the tenth.

* Reviews of titles followed by an asterisk will appear in a later number.

Diseases of Women. By TEN TEACHERS, under the direction of COMYNS BERKELEY, M.A., M.D., M.C. (CANTAB.), F.R.C.P. (LOND.), F.R.C.S. (ENG.). Pp. 558; 186 illustrations. Fourth edition. New York: William Wood & Co., 1930. Price, $6.00.

The present edition has been thoroughly revised and two new authors added to take the place of two who have resigned. The subject matter is brief and direct, such as would appeal to the medical student. It is an excellent manual of gynecology, including sections devoted to urinary and intestinal disorders and the psychologic aspect of pelvic disorders.

Diseases of the Nose, Throat and Ear. By WILLIAM LINCOLN BALLENGER, M.D., F.A.C.S. Revised by HOWARD CHARLES BALLENGER, M.D., F.A.C.S. Pp. 1138; 583 illustrations. Sixth edition. Philadelphia: Lea & Febiger, 1930. Price, $11.00.

This standard work has been thoroughly revamped where changes were indicated. These changes affect principally the chapters devoted to the sinuses, suppurative otitis media and mastoid disease. Dr. Chevalier Jackson and Dr. Gabriel Tucker have contributed a valuable section on endoscopy. The illustrations are clear and abundant, adding much to a work already of great value to the otolaryngologist.

Diseases of the Nose and Throat. By CORNELIUS G. COAKLEY, A.M., M.D., F.A.C.S. Pp. 672; 153 illustrations. Seventh edition. Philadelphia: Lea & Febiger, 1930. Price, $4.50.

This volume has for its primary purpose the provision of a compact manual of rhinology and laryngology for the student and practitioner. Brevity and clarity are maintained throughout and discussions of moot subjects avoided.

Manual of the Diseases of the Eye. By CHARLES H. MAY, M.D. Pp. 461; 374 illustrations. Thirteenth edition. New York: William Wood & Co., 1930. Price, $4.00.

The thirteenth edition of this very valuable little book contains an entirely new chapter on the use of the slit lamp. It is certainly one of the best ophthalmic primers in English.

Allergic Diseases: Their Diagnosis and Treatment. By RAY M. BALYEAT, M.A., M.D., F.A.C.P. Pp. 395; 87 illustrations. Third edition. Philadelphia: F. A. Davis Company, 1930. Price, $5.00.

The appearance of a new edition attests to the continued popularity of this book, primarily written for the layman, but gradually including more and more that will be found useful by the practitioner.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

Chronic Streptococcal Illnesses.—Many chronic illnesses are attributed to streptococci. These illnesses are usually bizarre, varied and differ in many respects. Some of them, as for example subacute bacterial endocarditis, are definite entities. The same thing applies to rheumatic fever, whereas other diseases are ones that are difficult to label. A person suffers from indefinite ill health; he may have secondary anemia or indefinite dyspepsia. These patients are those who are often found to have areas of focal infection which when removed clear up the general illnesses from which the patient is suffering. There may be also certain chronic local illnesses—surface infections, such as in chronic tonsillitis, chronic bronchitis and chronic sinusitis. PERRY (*Lancet*, London, 1930, p. 1009) notes that in all these conditions streptococci predominate, although the infection may be a mixed one. There is no specificity in the type of the streptococcus producing these lesions. Usually they are of the nonhemolytic or *viridans* group. They may be indifferent streptococci which have the peculiar property of acting as allergizing agents—a property not possessed by certain other microörganisms. As this is so, one is forced from both clinical and experimental data to conclude that the important factor in these chronic streptococcal illnesses is not so much the infecting streptococcus as it is how it enters the host, upon the host itself and the host's previous experience with different streptococci. Streptococci are unfortunately ubiquitous and once a person becomes hypersensitive to these organisms, various manifestations may take place. But little is known about bacterial allergy and immunity. When the difference between complete immunity, in which the patient is safe, and the dangerous state of allergy or hypersensitiveness, perverted immunity is appreciated, then only will practical treatment of these chronic streptococcal illnesses be discovered.

The Rôle of Staphylococci in Food Poisoning.—JORDAN (*Proc. Soc. Exper. Biol. and Med.*, 1930, **27**, 741) writes that the gastrointestinal type of food poisoning is usually considered due to the paratyphoid-enteritidis group of organisms. In fact, some Europeans do not attribute etiologic significance to any other organisms. During the past few years certain food poisoning outbreaks, apparently of bacterial origin, have been studied in his laboratory and thorough bacterial examination failed to disclose any paratyphoid bacilli. This has led the author to the conclusion that other bacteria may be responsible. Fortunately the opportunity occurred to try out this hypothesis. A yellow staphylococcus was apparently the organism responsible for the outbreak of food poisoning in Chicago. The sterile filtrates of 6 staphylococci were tested with human volunteers. From 5 to 10 cc. of sterile broth filtrates, when taken by mouth, produced in a few hours the customary symptoms connoting food poisoning. The staphylococci were of diverse origin. Three were isolated from normal human throats, 1 from a case of septicemia and 2 from food poisoning outbreaks. Twenty-six of the 34 volunteers developed these symptoms, while 11 controls taking the same food remained symptom-free. A second attack was produced by feeding a second portion of the material after a week's interval.

Observations on the Mechanism of Chlorid Retention in Pneumonia.—A heavy postcritical excretion of chlorid in pneumonia is frequently observed. Various explanations have been employed in order to explain this well-known phenomenon. GREENWALD (*Proc. Soc. Exper. Biol. and Med.*, 1930, **27**, 788) attacked the question from an angle which has not previously been tested. He found that in experimental pneumonia there is a very large increase in the excretion of chlorid on the first day, after which the output was much lower than in the control experiments. The author assumes that there is a similarly large excretion of chlorid the first day of pneumonia in man which would account for low concentration of chlorid in the blood and for a part of the marked retention usually observed. If this is true, as much as 8 gm. of sodium chlorid would be lost on the initial day of the disease, explaining why analyses of the tissues of patients dying from pneumonia have failed to show where the presumably retained chlorid was deposited.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

PHILADELPHIA, PA.

Diverticulitis of the Colon.—RANKIN and BROWN (*Surg., Gynec. and Obst.*, 1930, **50**, 836) say that diverticulosis is quite prevalent, apparently occurring in about 5 per cent of persons who have symptoms referable to the large bowel, but probably actually occurring in about 1 per cent

of all persons. Diverticulitis probably occurs in about 17 per cent of cases of diverticulosis and in most instances is chronic in its course and subject to exacerbations. The etiology of diverticula is obscure, but they are probably the result of several factors, among them inherent muscular weakness in the wall of the bowel and environmental conditions, obesity and constipation. Diverticulitis probably is the result of improper emptying of the bottle-shaped sacculations with subsequent inflammatory reaction, necrosis and occasional perforation. The relationship of diverticulitis to carcinoma probably is incidental rather than actual. In 227 cases reviewed in this paper as treated at the Mayo Clinic a malignant condition was found associated in 4 only. Diverticulitis occurs almost entirely in persons of middle age who are inclined to be corpulent and who lead sedentary lives. The outstanding symptom of diverticulitis is pain, usually situated in the lower left portion of the abdomen, and is frequently associated with constipation. Change in bowel habit is a confusing factor. Bleeding and tumefaction associated with diverticulitis are common and are usually the result of inflammatory reactions with or without the formation of abscess. In itself it does not indicate associated malignancy. In a definite percentage of cases diverticulitis tends to become complicated. The most common complications are abscess, fistula and perforation. The operation of choice is a graded procedure consisting of drainage with subsequent resection and anastomosis.

The Absorption and Transference of Particulate Material by the Great Omentum.—Higgins and Bain (*Surg., Gynec. and Obst.*, 1930, **50**, 851) state that a method is described for the study of absorption by the omentum isolated from all structures within the peritoneum. Studies have been made on the degree of absorption by the isolated omentum from the subcutaneous pouch at frequent intervals, ranging from thirty minutes to forty-eight hours after an injection. Lymphatic vessels within the omentum have not been demonstrated conclusively, and yet absorption from this organ is essentially by way of the lymphatics of the diaphragm and mediastinum It was not possible to demonstrate either free particles or graphite-like histiocytes in the omental bloodvessels following an injection into the subcutaneous pouch. Following phagocytosis of the graphite particles by active mobile histiocytes, these cells accumulate along the bloodvessels and pass toward the gastric and splenic attachments of the great omentum. The routes of drainage from the distal part of the omentum follow essentially the mesothelial lining of the lesser peritoneal sac. From the gastrocolic ligament, drainage follows around the dorsal surface of the stomach, along the lesser omentum, to the caudate lobe of the liver, and thence along the coronary ligament of the liver and the central tendon of the diaphragm to the anterior mediastinal lymph nodes.

Specificity of Light Action in Tuberculosis.—Phelps (*J. Bone and Joint Surg.*, 1930, **12**, 253) report that definite evidence of specificity of action occurs throughout the spectrum. The wave-length band lying between 320 and 380 millimicrons has been studied both clinically and experimentally. Effects have been obtained which prove this band to be active. The chief effect is an acceleration of the processes of repair

which may or may not be specific for tuberculosis, but which is essential in the retention of function. It is an indirect effect, general rather than local. The band between 320 and 380 millimicrons is found in all sunlight and in carbon arcs of 25 ampéres or more, using a carbon of known spectral distribution. Heliotherapy in tuberculosis can be as effectively carried out in sea-level towns as elsewhere. Longer exposures can be given if the erythema and tan-production rays, 300 to 320 millimicrons, are of small quantity or absent. Erythema and tan, therefore, are of no use as a basis of dosage given. Dosage should be measured in all sun therapy and the method of measuring such dosage is outlined. Artificial sources of light containing the band between 320 and 380 millimicrons and comparatively free from the shorter wave lengths are very useful as sun substitutes.

THERAPEUTICS

UNDER THE CHARGE OF

CARY EGGLESTON, M.D.,

ASSISTANT PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE, NEW YORK CITY,

AND

SOMA WEISS, M.D.,

ASSISTANT PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL, BOSTON, MASS.

The Medical Treatment of Spastic Conditions in the Alimentary Canal.—As a result of extensive investigations carried out by himself and by others whom he cites, LOEHR (*München. med. Wchnschr.*, 1929, **76**, 1869) finds that a combination of atropin, papaverin and a barbituric acid preparation is the most effective of all medicinal remedies for the relief of spasm both in the alimentary canal and elsewhere, such as in the bronchial tract, the gall bladder, biliary ducts etc. For this purpose he finds a tablet of the following combination to be most satisfactory: atropin sulphate 0.02; papaverin hydrochlorid 0.0005; diallyl barbituric acid 0.025. This tablet should be administered before meals in order to avoid the effects of the digestive secretions upon its components. The dose varies from ½ to 2 tablets repeated three times daily. The drugs comprised in this tablet diminish the hydrochloric acid secretion, allay spasm through both direct action and action upon the nerve endings and diminish pain through a mild general sedative action.

The Failure of Liver Therapy to Control the Cord Symptoms in Pernicious Anemia.—KRAUSE (*Klin. Wchnschr.*, 1929, **8**, 2177) reports conflicting evidences from the literature concerning the efficiency of liver diet in the control of the funicular myelitis of pernicious anemia. To these he adds the detailed reports of four of his own patients, all of whom showed a thoroughly satisfactory hematologic response to liver

diet. In none of these four patients however was there any improvement in the spinal cord symptoms. On the contrary, these symptoms either progressed as before the treatment or were apparently somewhat aggravated as a result of the administration of liver. From these and from similar cases reported by others, Krause suggests that the introduction of liver therapy by prolonging life in pernicious anemia may lead to an increased proportion of patients who show severe funicular lesions. He further suggests that the only favorable effect of the liver diet is that upon the blood picture while there is evidence that this diet is associated with some aggravation of the myelitis in certain cases.

Percutaneous Diphtheria Prophylaxis.—In the light of his previous investigations on tetanus toxin and in view of the fact that the injection of diphtheria toxin-antitoxin produces a fairly lasting period of hypersensitiveness to diphtheria, LOEWENSTEIN (*Klin. Wchnschr.*, 1929, **8**, 2283) finds, as a result of extensive experimentation upon animals, that a high degree of immunity to diphtheria may be produced by rubbing fairly large doses of active toxin through the epidermis in the form of a salve. The epidermis seems to have the capacity to detoxify such large doses without impairing their antigenic activity. The effectiveness of the inunction of such a salve as diphtheria toxin is proved by immunologic studies on animals as well as on man. When such protective ointment is administered to babies no untoward symptoms result and the blood serum rapidly develops a high antitoxin titer. Not only so, but investigations during epidemics of diphtheria seem to show that infants so treated possess an effective active immunity. The method seems particularly adapted to a large scale of prophylaxis.

The Action of Camphor on the Peripheral Vessels.—HEIMBERGER, in (*Klin. Wchnschr.*, 1929, **8**, 2238) points out that the new camphor substitutes which have been so strongly recommended for the treatment of severe cardiac and circulatory failure, have not shown any demonstrable improvement in results over the old camphorated oil. He also emphasizes that, in vasomotor paralysis associated with infectious and toxic processes, neither camphor nor the new camphor preparations have shown any satisfactory results. It is possible however that these agents may stimulate the heart and it has been suggested that they may have a similar stimulant action on the peripheral bloodvessels. With this thought in mind, Heimberger investigated the reactions in the capillaries and arterioles of the fingers in a group of patients to whom 20 per cent camphorated oil, cardiazol, hexeton, coramin and Hoechst's camphor solution were administered hypodermatically directly into the tissues of the finger being studied. These investigations showed conclusively that none of the agents exerted any specific stimulant action either upon the peripheral vasomotor nerves or directly upon the capillaries or arteriols. Furthermore, the reactivity of the capillaries was not altered. There is no evidence from these experiments indicating that these agents are capable of bringing about any improvement in the peripheral circulation. Since these studies were carried out upon normal individuals, it is impossible to transfer the results directly to those suffering from cardiac or vasomotor failure but there seems to be no good reason for believing that they would act differently in such patients.

The Treatment of Angina Pectoris with Muscle Extract.—SCHWARZMANN (*München. med. Wchnschr.*, 1929, **76**, 1798) reports a series of 7 illustrative cases out of a much larger series in which he employed an extract made from voluntary muscle for the treatment of angina pectoris. He selected such patients as had very severe angina, the attacks of which recurred at very frequent intervals, being brought on by the slightest effort or by overfilling of the stomach. In the majority of cases the muscle extract was given in doses of from 1 to 2 cc. Prompt relief of the painful seizures followed in most instances after the injection of 1 or 2 doses. The relief lasted from one to three or four days but when the doses were repeated at intervals of two to three days until several successive injections had been made, the relief frequently lasted for weeks. The relief of pain was the most striking response but, in addition, the patients frequently said that they were often completely free from all symptoms of cardiac distress. Such effects were often observed in patients whose symptoms had not been controlled by the usual methods of treatment, including the administration of the nitrites, the xanthins and morphin. In those having demonstrable evidences of coronary and aortic sclerosis excellent results were commonly obtained. The usual dose of the extract was 1 to 2 cc. The author does not offer any explanation of the probable mechanism by which the extract accomplishes these effects.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,

OF PHILADELPHIA.

Relative Prophylactic Value of Convalescent and Immune Adult Serums.—MORALES and MANDRY (*Am. J. Dis. Child.*, 1930, **391**, 214) found that the prophylactic use of convalescent measles serum with good results has been reported by various investigators, and that the use of immune adult serum has been encouraged, but they found little evidence in the literature regarding the true value of the serum derived from this source. In this report the authors present data which give adult serum a definite place in the prophylaxis of measles. They found that of 120 children exposed to measles by familial contact and immunized by the use of convalescent serum, 102, or 85 per cent, were completely protected. Fourteen of the 18 attacked in this group developed attenuated measles. Of 132 children exposed to the disease by familial contact, and immunized with doses from 20 to 40 cc. of immune adult serum, 108, or 80.3 per cent, received complete protection and 20 of 26, or 76 per cent, of those attacked developed attenuated measles. Doses of 10 and 15 per cent of adult serum gave complete protection in less than 50 per cent of the persons immunized, but usually resulted in an attenuated form of measles. Of 183 untreated children who were

utilized as controls, living in the same houses with patients who had clinical cases and with treated children, only 34, or 18.6 per cent, failed to contract the disease. Only 2 children had mild reactions among more than 500 who received treatment with serum. It would seem likely that a serious obstacle to the widespread use of convalescent serum will be the objection of some parents to the immunization of their children with blood obtained from strangers. Immune adult serum is readily and universally available, and the technique for obtaining it from adults or children who have had the disease is simple and does not involve any risk. Immune adult measles should be used with greater frequency for the protection of exposed children, especially for debilitated children who would probably die from the disease.

Asthma in Children.—PESHKIN and FINEMAN (*Am. J. Dis. Child.*, 1930, **39**, 1240) relate that in 15 children, from three to fifteen years of age, of whom 12 were sensitive and 3 were nonsensitive to protein, the asthma remained severe, persistent and of long duration in spite of treatment according to accepted standards of modern investigation and management. These children had been under observation for an average of two and a fifth years when selected for treatment with the ketogenic diets. No drugs, injections or other therapeutic measures were used. All foods recognized as possible causes of allergy in these patients were eliminated not only from the former diets, but also from the ketogenic diets. An estimation of the amount of food consumed by these children before the beginning of the ketogenic diet showed that they were all living on a high-carbohydrate diet. Average approximate ketogenic-antiketogenic ratio of the home diets ranged from 1 to 2 to 1 to 3. A maintenance diet or one of higher caloric value with a maximum ketogenic ratio of 3 to 1 was reached in all cases except one within three weeks, and after that the level was maintained for periods ranging from four to ten months. At the end of the third week of treatment 14 children, or 93 per cent, showed marked improvement or relief from asthma. Improvement was maintained for two months. After that and up to the tenth month 53 per cent were considered moderately to markedly improved or relieved from asthma. The ketogenic and low-carbohydrate diets alone do not appear to offer much promise of relief from pollen asthma or hay fever. In pollen asthma the administration of pollen treatment in conjunction with the ketogenic diet may prove of value. The results obtained cannot be ascribed to ketosis, as definite improvement or relief from asthma occurred in some children in whom acetone in the urine could not be demonstrated. The use of a maintenance diet or one of higher caloric value with a ketogenic ratio of 3 to 1 in the treatment of a child with chronic asthma who is underweight usually results in an appreciable gain in weight after a period of four months, while in a child who is obese the use of this diet usually results in a loss of weight, in spite of the fact that both types of children have been improved or relieved from asthma. Children with asthma and recurrent eczema on a ketogenic diet showed definite improvement from asthma but aggravation of the eczema. Children who had been free from eczema for several years prior to the institution of the low-carbohydrate high-fat diet did not have a recurrence of the rash in spite of the prolonged ketosis. The estimation of

the requirement in any given case was more easily determined from the formula of Pirquet. The food requirement is determined by multiplying the square of the sitting height in centimeters by the desired number of decinems. Multiplying by $\frac{2}{3}$ the number of calories is obtained. The maintenance diet is calculated at 4.5 decinems and a basal requirement at 3 decinems. The rapid control of asthma or relief from it resulting from the ketogenic diet possibly is brought about by some mechanism which involves a physicochemical change in the cells and blood of the patient, thereby inducing a partially or completely restored physicochemical or allergic balance.

Tuberculosis in Children.—Gross (*Arch. Pediat.*, 1930, **47**, 369) says that tuberculous infection in children is common, while tuberculous disease is not common. Of those infected, a great many, ranging from 50 to 70 per cent, go through life without getting tuberculous disease. Those children that get progressive tuberculous disease in early infancy and childhood usually succumb. Some infants with active tuberculosis do recover. This disease in children is universal and is not confined to any particular sections of the country. Most of the tuberculosis in children belonged to the primary and secondary stages. Physical signs in the lungs are not necessarily the result of tuberculosis, and the clinical history, tuberculin reaction, the fluoroscope and the Roentgen ray must all be considered in arriving at a diagnosis. The reduction of the morbidity and the mortality of tuberculosis is of the utmost importance. The work must begin in childhood.

The Brain-liver Weight Ratio and the Infancy and Childhood History of Epileptics.—Weingrow (*Arch. Pediat.*, 1930, **47**, 392) states that in all types of epileptics the average brain and liver weights vary from those found in the normal. In the idiopathic division, as well as in the symptomatic group without causal postmortem finding related to the epilepsy, and also in the undetermined class, the average brain weight falls below normal in the greatest number of cases. In the nonidiopathic division, with postmortem findings casually related to the epilepsy, the subnormal and the supernormal cases approximate each other. The number of cases in which the liver is below that found in the normal exceeds the number of instances in which this organ showed a normal and supernormal weight in all types of epilepsy described. The greatest percentage of epileptics with liver weights below normal is found in the symptomatic and undetermined groups. The average birth weight of individuals in the essential group does not differ from that in symptomatic division, and the averages of both fall within normal limits. The average age incidences of teething, walking and talking show no appreciable differences in the symptomatic and essential individuals, and their average age range incidence is within that of the normal. The intelligence of the epileptics in the idiopathic division, as judged by the average age at which the individuals commenced and terminated their education and by the grade they reached does not differ from that of the symptomatic division. Measles, pertussis, scarlet fever and diphtheria in the essential present no difference from the symptomatic class of epilepsy. With the brain weights subnormal, normal and hypernormal there seems to be no relationship to

the congenital, developmental or infectious factors mentioned in both the symptomatic and essential classes of epileptics. All groups present evidences of mental impairment as the disease progresses. In the essential epilepsy the mental impairment does not differ markedly from that in the symptomatic group. The brain weight variations have no influence upon the intellectual decline of these individuals in the three types considered.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.,

PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA,

AND

VAUGHN C. GARNER, M.D.,

ASSISTANT PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA.

Lichen Spinulosus Following Intradermal Application of Diphtheria Toxin.—BECKER (*Arch. Dermat. and Syph.*, 1930, **21**, 839) stresses the fact that lichen spinulosus is a morphologic term and represents a type of follicular reaction. The acute type may be a form of trichophytid, a form of arsphenamin dermatitis, or due to unknown causes. The chronic varieties are represented by spinulous lichen scrofulosorum, the spinulous type of follicular syphilid and lichen ruber planus. Certain of the chronic forms are recurrent or permanent. The spinulous characteristics may appear as part of another dermatosis. The author has seen such examples in a toxic dermatitis following the administration of gold sodium thiosulphate and in perifollicular seborrheic dermatitis of long-standing. A case is reported in which lichen spinulosus followed a positive Schick reaction in a boy of six years. The author concludes that the follicular apparatus may act collectively as a unit in response to certain noxæ comparable to the epidermal cells in eczema and the superficial vascular system in erythemas, scarlatiniform dermatitis and in urticaria.

Coccidioidal Granuloma: A Clinical and Experimental Review With Case Reports.—JACOBSON (*Arch. Dermat. and Syph.*, 1930, **21**, 790) discusses his observations and treatment in 19 cases of coccidioidal granuloma. The previous use of such measures as Roentgen rays, surgery, iodids and intravenous dyes have all be unsatisfactory. The author has employed a colloidal copper and coccidiodin-B with good success except in the acute fulminating type of the disease. This latter type is generally closely associated with the occurrence of face lesions. The author's technique includes deep gluteal injections of the colloidal copper every four to seven days and the cutaneous injection of coccidiodin-B every eight to fourteen days. In selected cases isolated cutaneous lesions may be treated with carbon-dioxid snow. Thirteen cases are reported in detail.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

CHARLES C. NORRIS, M.D.,

PROFESSOR OF OBSTETRICS AND GYNECOLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.,

AND

FRANK B. BLOCK, M.D.,

ASSOCIATE IN GYNECOLOGY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

Time of Ovulation.—A rather detailed investigation has been made by OGINO (*Zentralbl. f. Gynec.*, 1930, **54**, 464) of Japan into the determination of the time of ovulation and conception with relation to the menstrual cycle. The statistics presented are based upon observation on 118 patients whose ovaries were carefully observed during laparotomy. Of these patients, 81 had a regular menstrual cycle while in the other 37 the periods were irregular. By means of elaborate tabulations he shows that the time of ovulation is a five-day period which comes from twelve to sixteen days before the next menstrual period. By dating the time of ovulation from the next expected period rather than from the last preceding one, a more exact statement can be made, expecially in those patients whose menstrual cycles are irregular. In regard to the time of conception, he finds that it is usually during an eight-day period which occurs between the twelfth and nineteenth day preceding the next period, or in other words during the five-day ovulation period and the three days preceding it. During the period of twenty to twenty-four days preceding the menses conception rarely occurs, while during the period of one to eleven days preceding the menses he believes conception is impossible. From a practical standpoint this would mean that a woman becoming married before or during the ovulation time might become pregnant without having any mentrual periods following such marriage. On the other hand if marriage occurs after the time of ovulation it is practically impossible for the woman to become pregnant before she has had a menstrual period. This study indicates that the possibility of impregnation of the human ovum is quickly lost after ovulation.

Prognosis of Uterine Cancer.—As the result of his extensive experience at the Memorial Hospital in New York, HEALY (*N. Y. State J. Med.*, 1930, **30**, 191) is of the opinion that the early clinical diagnosis of uterine cancer is the most important factor in the prognosis. Grouping of tumors according to cell type based on Broders' classification is important as a guide to correct treatment and therefore a protection to the patient, especially if the treatment contemplated is surgical. He has found that the prognosis and end-results in uterine cancer vary according to whether operation or radiation therapy is the method employed. With operation, all group 4 cases (Broders' classification)

give uniformly bad results, whereas with efficient radiation therapy the results are surprisingly good, 66 per cent of the favorable cervix cases and 50 per cent of the favorable corpus cases remaining well five or more years. It is absolutely essential that a preliminary study of the histologic structure of the tumor be made from a biopsy specimen or material obtained by curettage in order to determine the kind of therapy that should be employed. While advanced cases which form 80 to 85 per cent of all cases of cervical cancer are entirely beyond the help of surgery, it is interesting that under radiation therapy 23 per cent of his advanced cases were alive at the end of five years. To those who have been following this subject, this figure will appear as probably one of the best yet published in this type of case and shows that progress is certainly being made even though at times such progress seems exceedingly slow.

OPHTHALMOLOGY

UNDER THE CHARGE OF

WILLIAM L. BENEDICT, M.D.,

HEAD OF THE SECTION OF OPHTHALMOLOGY, MAYO CLINIC, ROCHESTER, MINN.

Plasmoma of the Conjunctiva in China.—Plasmoma of the conjunctiva being a relatively common disease in China, SOUDAKOFF (*China Med. J.*, 1930, **44**, 195) has had an opportunity to observe the disease from its very early stages to very late in its course. Seventeen of these cases were observed both clinically and histopathologically. At the onset it begins clinically as a small growth of the fornix or plica which gradually spreads over the palpebral and bulbar conjunctiva; it may even involve the cornea. Histologically it appears as a diffuse plasma cellular infiltration, beginning either directly beneath the epithelium or separated from that by a strand of connective tissue which is more or less normal. Plasmoma is not a tumor, but rather a reaction to a chronic inflammation caused by some irritant. Thus, the majority of the patients showed trachoma; the author believes that trachomatous toxins act as an irritant. The plasma cellular infiltration prevents the destructive action of the toxins on deeper tissues. Their prolonged action may lead to advanced hyalin-amyloid degeneration of the connective tissue. The treatment recommended by the author is early excision followed by radium irradiation.

Herpes Ophthalmicus Febrilis With Dendritic Keratitis Complicating Therapeutic Malaria.—During a course of therapeutic malaria administered to a patient suffering from cerebral syphilis the cornea of the left eye showed a herpetic eruption, which soon progressed to a definite dendritic type of keratitis; at the same time there was herpes outlining the infratrochlear nerve on the left side of the nose. When admitted to the hospital the patient complained of a visual defect of several years' standing; it was found to be a left superior quadrantic homonymous anopia. The patient was inoculated with tertian malaria and

had six paroxysms. After the fourth he complained of a foreign body in the left eye, which on examination was found to be a circumcorneal injection with lachrymation and photophobia. There was sharp, lancinating pain; the symptoms became worse with each chill. On the third day small vesicles appeared over the temporal margin of the cornea; a pressure bandage was applied and the malaria discontinued. On the sixth day herpetic vesicles appeared along the infratrochlear nerve. Other vesicles appeared to coalesce with those on the cornea, and in a short time there was evident ulceration of the branching or dendritic type. The nasal herpes quickly dried when quinin was given, but the ulceration of the cornea persisted. Atropin sulphate and quartz light therapy did not clear it up. It was found that the recrudescence of the disease occurred a day or two after the administration of neoarsphenamin. As soon as this was stopped there were no more flareups and the corneal clouding diminished markedly. Vision is still partially obstructed, however; there are no changes in the visual fields. EBAUGH and JEFFERSON (*Arch. Neurol. and Psychiat.*, 1929, **22**, 1226) state that the absence of other signs of arsenic poisoning throws some doubt on their deduction of the relation of the neoarsphenamin to the herpes. On the other hand, herpes simplex has been known to occur in arsenic poisoning. The condition is important, as it is an indication for immediate cessation of the malarial treatment; it may result in permanent visual defect; relapses may occur during postmalarial, arsenic therapy.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF
DEWAYNE G. RICHEY, B.S., M.D.,
MERCY HOSPITAL, PITTSBURGH, PA.

Further Observations on Dental Caries as a Contributing Factor in Maxillary Sinusitis.—On a previous occasion,[1] Berry estimated that 60 per cent, and conceivably 80 per cent, of patients with paranasal sinus disease would show some form of dental caries in the antral bony floor. To his original series of 152 cases, BERRY (*Arch. Otolaryngol.*, 1930, **11**, 55) adds 73 cases of which 59 per cent had a demonstrable abscessed infection of a root of a tooth just below the involved antrum. The author again outlines the technique of ascertaining dental caries in connection with maxillary sinusitis by transillumination and reiterates his plea that the "careful rhinologist must consider gross dental pathology."

The Effect of Camphor, Eucalyptol and Menthol on the Nasal Mucosa.—As reported in a former article (*Arch. Otolaryngol.*, 1927, **6**, 112), Fox, learned from a series of experiments on clinical patients and laboratory animals that menthol was more irritating to the nasal mucous membranes than camphor or eucalyptol. In a subsequent publication (*Arch. Otolaryngol.*, 1930, **11**, 48) Fox illustrates by photomicrographs the actual anatomic changes encountered in the nasal

[1] *Vide* retrospect: AM. J. MED. SCI., 1929, **178**, 143.

mucous membranes of rabbits sprayed once daily for nine months with liquid petrolatum solutions of menthol, camphor or eucalyptol. The experiments were designed to parallel the usual application of these drugs in practice. All materials for microscopic study were obtained at autopsy. When applied to the nasal mucous membrane of a rabbit for nine months, it was found that, whereas menthol used in dilutions as low as 1 per cent caused some degenerative changes, the same drug in 5 per cent dilutions produced definite destructive changes throughout all layers of the Schneiderian membrane. Deleterious effects were also noted following the similar administration of 5 per cent camphor, 5 per cent eucalyptol and even liquid petrolatum. Since some of the animals in each group exhibited pulmonary abscesses, the author is of the opinion that these abscesses were possibly aspiration phenomena occurring during the intranasal spraying.

Repair in the Paranasal Sinuses of Man Following Removal of the Mucous Membrane Lining.—Sufficient clinical evidence as accumulated in recent years to show that certain persistent infections of the paranasal sinuses necessitate surgical removal of the involved mucosal lining. Moreover, it has been observed that subsequent repair occurs with variable results. Inasmuch as the exact nature of the new tissue has never been determined, SEMENOV and KISTNER (*Proc. Soc. Exper. Biol. and Med.*, 1930, **27**, 322) subjected to histopathologic examination the mucous membranes of human antra from which varying amounts of the mucosa had been removed at former operations. In two instances in which almost one-third of the antral mucous membrane had been removed two years previously, microscopic sections showed the original portion of the lining to consist of such normal histologic structures as: (1) a layer of pseudostratified ciliated columnar epithelium; (2) a superficial spongy layer of areolar connective tissue with large tissue spaces; (3) tuboalveolar mucous and serous glands in the layer of loose connective tissue; (4) an orderly arrangement of branching arteries and arterioles in definite layers, and (5) a definite periosteal layer of compact connective tissue. The repaired portion, on the other hand, consisted (1) of a thick mass of fibrous scar tissue covered for the most part by an indifferent layer of cubical epithelium which was stratified in some places and entirely absent in others; (2) of an irregular vascularization of the scar tissue, and (3) an absence of the usual mucosal architecture, as well as of the glands. Following complete subperiosteal exenteration of the antral mucous membrane it was observed in 2 cases—eight and eighteen months after the primary operations, respectively—that there was a marked thickening of the bony walls and that the antra were lined by a thick, dense layer of scar tissue which was firmly adherent to its subjacent structures and was covered by stratified columnar epithelium when epithelization extended from the nasal mucosa or by stratified squamous epithelium when it extended through an opening in the canine fossa. Abundant regeneration of glands occurred in those cases where the reparative process began from the flap of Schneiderian membrane brought through the fenestrum in the nasoantral wall. This observation is in accord with experimental findings on dogs (Knowlton and McGregor).[1]

[1] *Vide* retrospect: AM. J. MED. SCI., 1929, **178**, 144.

RADIOLOGY

UNDER THE CHARGE OF

ALBERT MILLER, M.D.,

AND

CHARLES G. SUTHERLAND, M.D.,

CONSULTING PHYSICIANS, SECTION OF ROENTGENOLOGY, MAYO CLINIC, ROCHESTER, MINN.

Calcification of Intrathoracic Exudates.—Certain observers incline to the theory that tuberculosis is largely responsible for calcified intrathoracic exudates, but there are others who hold that the cause is nontuberculous. ANDERSON (*Am. J. Roent. and Rad. Therap.*, 1929, **22**, 531) reports three cases favoring the claims of the latter group. One was a case of interlobar pleurisy, the second a case of calcified exudate along the left ventricle of the heart and the third a case of pericarditis calculosa. This is the nineteenth recorded case of pericarditis calculosa diagnosed during life.

Ultraviolet Radiation Therapy in Erysipelas.—Presenting data from 91 cases of erysipelas treated by ultraviolet light, UDE (*Radiology*, 1929, **13**, 504) advocates the method as universally applicable because it is readily available, requires but one treatment, is devoid of danger, is inexpensive, and the results are comparable to those of any other method. The technique is simple and can be carried out with any ultraviolet lamp. Ude employs a distance of 8 inches. The exposure time varies with the efficiency of the lamp and should represent twice the time required to produce a mild erythema on normal skin. Local applications of magnesium sulphate solution or other substances are not permitted following irradiation.

A Study of the Halogenated Oils Employed in Roentgenology.—For several years iodized oils have been employed to great advantage for the roentgenographic and roentgenoscopic visualization of certain body cavities. The iodized oils, however, are unstable toward heat, light and moisture; the iodin or iodids subsequently always liberated in the body may, over long periods of time, cause toxemia, irritation, or iodism; their cost is considerable, and their viscosity is so high that they are frequently ill suited for the particular purpose. Accordingly, TABERN, HANSEN, VOLWILER and CRANDALL (*Radiology*, 1930, **14**, 364) have undertaken the development and study of brominized oils and esters as substitutes for the iodin mixtures. Two products have been found to possess the most desirable properties. The first was 33 per cent brominized olive oil esters (viscosity, seven seconds) and the second a mixture of 85 per cent brominized olive oil and 15 per cent of brominized olive esters (viscosity, one hundred and twenty seconds). For filling nasal accessory sinuses the brominized olive esters are preferable; filling is rapid and complete and the time of drainage is

reduced by many hours. The ester product is also superior for visualization of the seminal vesicles and has been used successfully for pyelography. It was introduced into the uterus and Fallopian tubes, and little pressure was necessary, but the tubal shadows were less distinct than with oils of higher viscosity. For visualization of the bronchial system the second mixture is preferable. The brominized oils and esters are more stable than the iodized oils, have controllable viscosities without loss of radiopacity, are economical to manufacture and use, low in toxicity and, of course, cannot cause iodism.

The Roentgenologic Manifestations of Intracranial Disease.—In order of their importance the various roentgenologic signs of intracranial disease are grouped by CAMP (*Radiology*, 1929, **13**, 484) as follows: (1) Calcification within the lesion itself; (2) localized changes in the bone, such as destruction, proliferation or both; (3) changes in the sella turcica; (4) changes in the bone from increased intracranial pressure; (5) displacement of the pineal shadow; (6) air in or about the lesion; (7) increased vascularity of bone. Lesions that may exhibit calcification include tumors, hematomas, tubercles, cysts, old abscesses, old meningeal lesions, encephalitis, sclerotic arteries and aneurysm. Such calcification requires distinction from the calcification which often occurs normally in the pineal gland, choroid plexus and Pacchionian bodies. The bones of the skull overlying a contiguous tumor may exhibit locally the changes of destruction, proliferation or both. Most often the change consists of thinning of the internal table. Hyperostosis may occur, especially in association with parasagittal tumors and those that arise from the temporofrontal meninges. Lesions causing deformity of the sella turcica include benign and malignant tumors of the pituitary gland, extrasellar tumors giving rise to increased intracranial pressure, and disease of the sphenoid bone. Displacement of the shadow of the pineal gland is valuable in the diagnosis and localization of intracranial tumors. Increased vascularity of the bone is likely to accompany angiomatous tumors of the cortex. The value of the foregoing signs has been variously appraised. Crouse from a review of the literature estimated that 8 per cent of the lesions of the brain can be diagnosed from the roentgenogram. Dandy computed that 15 to 20 per cent can be localized. Sosman, reviewing the main groups of tumors, was able to identify the tumor by means of the Roentgen ray alone in 37 per cent.

Interpretation of Gastric Symptoms.—The conclusions drawn from a study of 3000 consecutive patients requiring a gastrointestinal examination are presented by DWYER and BLACKFORD (*Radiology*, 1930, **14**, 38). It is well known that the majority of patients who complain of gastric symptoms do not have organic disease and this is corroborated by the present series. Only 15 per cent of the patients had organic lesions of the stomach or duodenum to account for the symptoms. Duodenal ulcer was found in 8.1 per cent and was the most common organic finding in the stomach or duodenum. Gastric ulcer was only a fifth as common as duodenal ulcer. Cancer was found in 3.6 per cent of the patients who had gastric symptoms; 80 per cent of the cancers apparently originated in a resectable area of the stomach. Disease of

the gall bladder was the most frequent cause of the symptoms, and was regarded as responsible for the dyspepsia in 21.3 per cent. In 59 per cent of all cases the cause of the dyspepsia was not due either to functional or organic conditions in the stomach, duodenum or gall bladder.

Infraclavicular Foci of Infiltration as Evidence of Incipient Tuberculosis in Young Adults.—During the last eight years ASSMANN (*Radiology*, 1930, **14**, 93) has encountered what he believes to be a characteristic type of pulmonary lesion in the early stages of tuberculosis of the lungs, particularly in young adults. The lesion, as seen with the Roentgen ray, consists as an isolated rounded focus of varying density, usually situated just below the clavicle, in the lateral part of the pulmonic field, more rarely in the upper portion of the lower lobe. Such a lesion is usually sharply circumscribed and definitely contrasted, but it may have little density and show a gradual transition into the normal pulmonic field. It is of fundamental importance to understand that, in contradiction of the generally accepted idea that tuberculosis of the lungs nearly always begins in the apices, the type of lesion described, the infraclavicular focus, is associated with absolutely normal apices. From this focus a general tuberculosis may develop, but with timely treatment a favorable prognosis may be given.

Radium in the Treatment of Disease with Subcutaneous Mucosal Hemorrhages.—Five cases are reported by HOFFMAN (*Radiology*, 1930, **14**, 136), comprising 2 of umbilical hemorrhage, 2 of purpura hemorrhagica and one of hemorrhage after circumcision in all of which radium treatment of the spleen was given. Save in one of the cases of umbilical hemorrhage, bleeding was stopped and in both cases of purpura hemorrhagica the disease has not recurred. The author concludes that radium offers a new and valuable aid in the treatment of hemorrhagic diseases of the newborn, as well as in simple purpura hemorrhagica. In hemophilia radium will help in controlling the severe hemorrhages without other medication. He warns that if the total erythrocyte count is below 1,000,000 this method must be used very cautiously because of the hemolytic action of gamma rays, and preliminary transfusions should be given to bring the blood count above that level.

The Roentgen Treatment of Morbus Basedowii.—HOLZKNECHT (*Radiology*, 1930, **14**, 139) points out that since 1904 it has been known that morbus basedowii can be cured by Roentgen ray treatment, about 60 per cent of cases showing cure and about 20 per cent improvement to a greater or less degree. He concedes that a very acute case of the disease should be operated on because of the quick relief which ensues. Cases not responding to Roentgen ray therapy and those with signs of tracheal compression by a large nodular struma should also be operated on. But there is no reason at all for giving up local treatment of the thyroid, and there is no basis whatsoever for resorting to general skin treatment with grenz rays, as advocated in certain quarters. As to the rays producing adhesions which render subsequent operation difficult, statistics prove that adhesions, if found, were already there before treatment, and that they occur just as often in untreated as in treated cases.

Roentgen Ray Diagnosis and Therapy of Thyroid Disease.—The Roentgen ray, properly applied, is a safe therapeutic agent in thyroid disease, according to REMER and BELDEN (*Radiology*, 1930, **14**, 145). Certain cases of toxic goiter should be given the benefit of irradiation for at least four treatments, continuing it if improvement is noted, and referring the case to surgery if no improvement occurs. Radiation does not increase the difficulty of subsequent operation. Radiation before operation renders a patient a better surgical risk. The danger of hypothyroidism is negligible. The basal metabolism test is an important adjunct and the treatment should be governed by it. Severe cases should be hospitalized and a period of rest obtained before treatment is begun and after the first one or two exposures.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

FRANKLIN G. EBAUGH, M.D.,

PROFESSOR OF PSYCHIATRY, UNIVERSITY OF COLORADO, DENVER, COLORADO,

AND

GEORGE JOHNSON, M.D.,

INSTRUCTOR IN PSYCHIATRY IN THE UNIVERSITY OF COLORADO.

The Distribution of Nonelectrolytes Between the Blood and the Cerebrospinal Fluid.—COCKRILL (*J. Nerv. and Ment. Dis.*, 1930, **71**, 443) presents a discussion of the theories of the nature of the cerebrospinal fluid. He selects urea distribution between the blood and cerebrospinal fluid as being of the greatest significance because of the accuracy of determination and the fact that there is no reason to believe that urea is either consumed or produced by any part of the nervous system or adjoining tissues, and because of its ready diffusibility and solubility. He calls attention to the fact that the cerebrospinal fluid water consistently contains less urea than that of the blood plasma. He believes that the discrepancy would be even greater if the water content of the two fluids were taken into consideration by the investigators. Experiments on cats showed that with an accumulation of urea in the blood the urea concentration of the cerebrospinal fluid increased at approximately the same rate, the discrepancy in distribution remaining the same. Dialysis experiments *in vitro* indicated that under these conditions there was a tendency for the urea concentration to equalize between the blood plasma and cerebrospinal fluid. He considered these results as evidence against the view that the cerebrospinal fluid is produced solely by ultrafiltration of the plasma.

Huntington's Chorea Without Choreiform Movements.—CURRAN (*J. Neurol. and Psychopathol.*, 1929–30, **10**, 305) presents a case of Huntington's chorea exhibiting the typical hereditary characteristics, and occurring in several members of the family, in only one of which were

choreiform movements present. Dysarthria was the only motor symptom manifest in the majority of the cases, but marked mental deterioration was common in all. Two members of the family had been diagnosed as cases of general paresis, and the case presented had points of similarity with this disease. It is pointed out that the complete absence of motor symptoms does not necessarily negative the diagnosis of the disease. Stress is placed on the distinctive heredity and the differential diagnosis.

A Case of Decerebrate Rigidity With Autopsy.—EPSTEIN and YAKOVLEV (*J. Neurol. and Psychopathol.*, 1929–1930, **10**, 295) reveals a case of decerebrate rigidity first observed in a child at the age of two years and seven months, and under observation until death, at the age of eight years and three months. The case in history and physical findings is typical of cerebral infantile tetraplegia of congenital or immediately postpartum origin. The neurologic findings were typical of decerebrate rigidity with the tonic neck reflex of Magnus and de Kleijn, extensor rigidity, pseudoaffective reactions and tonic fits. Pathologic study resulted in the anatomic diagnosis of microcephaly and microgyria, cerebral aplasia with absence of corpus callosum, aplasia of the cerebellum and the basal ganglia, degeneration of the thalamus, diffuse gliosis and corticospinal tract degeneration.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

PROFESSOR OF BACTERIOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA,

AND

W. L. HOLMAN, M.D.,

PROFESSOR OF BACTERIOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA.

Contribution to the Study of the Sympathetic Nerves of the Appendix: The Musculonervous Complex of the Submucosa.—MASSON (*Am. J. Path.*, 1930, **6**, 217), while studying nerve proliferation in the appendicular mucosa and the origin of carcinoid tumors, acquired the idea of a submucous musculonervous complex. This article deals fully with the latter mechanism as studied in different types of appendices. The so-called "complex" is made up of fine bundles of muscle tissue, which separate themselves from muscularis mucosæ and pass into submucosa, where they anastomose with similar fibrillar bundles, passing off obliquely from the inner circular muscle of the same sector of appendix. These muscle elements are very intimately associated with the nerves of Meissner, which are always present between the muscle network. The most typical structure is noted in the submucosa of appendices of the newborn. This "normal" type is maintained in healthy adult

appendices. But in appendices showing the results of repeated crises, characterized by extreme diminution of lymph nodules, thickened walls and narrowed lumen, the muscle bundles of the complex are hypertrophied, as are the elements of Meissner's plexus. Accompanying this change the walls of the vessels, including the intima, are thickened. Various gradations of hypertrophy and hyperplasia are noted, the most extreme presenting small neuromata throughout the mucosa as well as hypertrophy of both elements of the complex within the submucosa. The significance of the musculonervous complex described is obscure to the author. In the discussion it is suggested that in the appendix two groups of nerves are found, the argentaffin group and the myenteric group.

Spontaneous Tuberculosis in the Guinea Pig.—GRIFFITH (*J. Path. and Bact.*, 1930, **33**, 153) has found that spontaneous tuberculosis occurs but rarely in the guinea pig. Of 7 strains examined by him from cases of spontaneous tuberculosis, 6 were bovine and 1 human. He further reports what apparently are the first recorded examples of spontaneous avian tuberculosis in guinea pigs. The lesions produced by the avian bacilli differ from those usually found when mammalian strains are inhaled, in that the tracheobronchial glands are enlarged, but show no fibrotic thickening and contain purulent rather than caseous material.

The Local Effect of the Injection of Gases Into the Subcutaneous Tissues.—While gases have been previously injected into the body, WRIGHT (*Am. J. Path.*, 1930, **6**, 87) is apparently the first to report on the result of subcutaneous injections of gases, particular attention being paid to the local tissue reactions. The studies were conducted in close association with studies upon tuberculosis where large numbers of monocytes and epitheloid cells were noted as the chief tissue reaction. A similar reaction was observed following the injection of yellow phosphorus. These experiments were carried out to determine whether or not this reaction was due to a common chemical etiology or if it was purely physical and nonspecific. Small amounts of sterile oxygen, nitrogen and carbon dioxid were introduced at different intervals, depending upon the rates of absorption and sections from the altered areas studied. The results showed that, following an immediate acute reaction, there were produced in the injected tissues large numbers of monocytes, modified monocytes, epitheloid cells and giant cells. The reaction, due to nonspecific causes is similar to that seen in tuberculosis and occasional histologic structures closely resembling tubercles were observed. The authors believe that the monocytes present arise locally "from some type of fixed connective-tissue cell," and that, in turn, the epitheloid and giant cells originate from the monocytes. The cellular analyses are described and protrayed in detail.

Osteogenesis Imperfecta Congenita.—WEBER (*Arch. Path.*, 1930, **9**, 984) reports a case of osteogenesis imperfecta in which the triad of symptoms necessary, according to von Recklinghausen, are fulfilled. He attempts in his analysis of the case to determine at what stage in the development of bone the changes peculiar to osteogenesis imperfecta

arise. He uses as a basis, stages in bone development outlined by himself in a previous article. He finds that while the formation of mesenchymal tissue, osteoid tissue and chondroid tissue proceeds along normal lines, the entire bone-producing system is arrested in the "nucleus" stage, the stage in which the intercellular substance becomes calcified, forming nuclei for the latter deposition of lamellar bone. The bone present consists of "fiber" bone of an inferior quality. True lamellar bone is completely lacking, and osteoclasts are entirely absent except in the region of callus formation.

Antibacterial Action in Cultures of Penicillium, With Special Reference to Their Use in Isolation of Bacillus Influenzæ.—FLEMING (*Brit. J. Exper. Path.*, 1929, **10**, 226) describes the action of a substance, which he calls penicillin, contained in the filtrate of a broth culture of a strain of a penicillium. This substance inhibits the growth of the Gram-positive cocci of the mouth (staphylococcus, streptococcus and pneumococcus), while the other oral organisms are practically unaffected, especially Bacillus influenzæ. By planting throat swabs on chocolate-agar plates, and smearing 6 to 8 drops of penicillin over half of the plate, the author has easily isolated this organism, even though it was present amid multitudes of staphylococci and streptococci. In a more recent article (*Brit. J. Exper. Path.*, 1930, **11**, 127), in conjunction with MACLEAN, the author records having found Bacillus influenzæ in cultures made from the gums of 30 normal individuals by means of penicillin.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE, WASHINGTON, D. C.

The Rôle of the Vaccination Dressing in the Production of Postvaccinal Tetanus.—ARMSTRONG (*Pub. Health Rep.*, 1929, **44**, 1871) arrives at the following conclusions: (1) Tetanus as a complication of vaccination against smallpox is confined, as far as we are aware, to primary "takes" in which some type of dressing was strapped to the vaccination site. (2) Evidence is produced which indicates that in postvaccinal tetanus the specific organism gains entrance to the vaccination through an accidental infection from extraneous sources. (3) Evidence is produced which indicates that a deep implantation of Bacillus tetani in the devitalized components of the "take" is necessary before postvaccinal tetanus will develop. (4) A dressing strapped to a

cutaneous vaccination permits this deep implantation of organisms by producing severe "takes," and by retaining exudate therefrom at the vaccination site. (5) Injection methods of vaccination such as the intracutaneous technique are suitable methods for the experimental production of postvaccinal tetanus and would seem to be, from the standpoint of this complication, a potentially dangerous method for human use. (6) The freedom of openly treated cutaneous vaccinations from the complication is explained by the continued wiping and ventilating action occasioned when the arm is moved within the sleeve or under the bed clothes. This light friction keeps the vesicle dry and firm, and thus either prevents or promptly wipes away any exudate which may appear. (7) A small, superficial implantation of the virus, as recommended in the multiple pressure technique advocated by Surgeon J. P. Leake, and the abandonment of dressings fixed to the vaccination site will eliminate tetanus as a complication of vaccination. If a dressing is deemed advisable for any reason, the objectionable feature of the *fixed* covering can be avoided by pinning a few layers of gauze to the inside of a loose-fitting sleeve.

Experimental Epidemiology of Tuberculosis.—Normal guinea pigs confined with tuberculous cage mates were found by Perla to acquire tuberculosis of alimentary origin, characterized by a marked involvement of the mesenteric and cervical lymph nodes. Guinea pigs confined in the same room with tuberculous animals but not in the same cage acquired a disease of respiratory type, characterized by extensive lesions of the lungs and of the tracheobronchial lymph nodes. The incidence of the disease increased with the intensity and duration of the exposure. His work did not, however, show conclusively the effect of crowding upon the incidence of "contact" tuberculosis, because the intensity of exposure in his experiments was not the same in each degree of crowding. Perla's studies have been continued by LURIE (*J. Exper. Med.*, 1930, **51**, 729). In judging these experiments it must be borne in mind that the experimental epidemiology of tuberculosis entails greater difficulties than a similar study of a more acutely fatal disease. The laborious nature of the experiments, extending over long periods of time, the chronicity of the disease, the relatively low incidence of tuberculosis acquired naturally by guinea pigs precludes the rapid demonstration of facts. The author found that if normal guinea pigs are confined with an equal number of tuberculous cage mates the incidence of "contact" tuberculosis is increased by crowding. This is probably due largely to an increase in the amount of tubercle bacilli available in the more crowded cages, although no constant relationship could be established between the intensity of the exposure and the incidence of tuberculosis acquired by contagion. Other factors must be determined. If guinea pigs are inoculated intraperitoneally with a given quantity of human tubercle bacilli, and distributed in different degrees of crowding, the duration of survival is shortened in the more crowded animals, and the incidence of chronic types of tuberculosis is greater among the less crowded animals. Guinea pigs living in the same room but not in the same cage with tuberculous animals acquire tuberculosis, characterized by a chronic course, a marked involvement of the lungs, often with cavity formation and a massive tuberculosis of the tracheobronchial

nodes; the mesenteric and cervical nodes are slightly or not at all affected. The route of infection in these guinea pigs is almost always the respiratory tract. Of 103 guinea pigs exposed for a period of up to thirty-two months, 15, or 14.5 per cent, developed tuberculosis. The shortest period of exposure leading to fatal tuberculosis was eight months. The incidence of this tuberculosis acquired by air-borne contagion increases with the duration and intensity of the exposure up to a certain point. A large percentage of the guinea pigs weathered a continuous exposure to the tubercle bacillus for thirty-two months without becoming tuberculous. This may be due to an innate natural resistance against tuberculosis, or to an acquired immunity resulting from the continuous exposure to the contagion. If normal guinea pigs are confined with tuberculous cage mates in cages where the food becomes contaminated with the excreta, laden with tubercle bacilli, of the inoculated animals, the incidence of acquired tuberculosis among them is greater than among guinea pigs similarly exposed in cages where this mode of infection is largely eliminated. The disease acquired in the first type of cage is largely of enteric origin and is chronic in type. The disease acquired in the second type of cage is of respiratory origin and has a more acute course. In tuberculosis of guinea pigs acquired by contact with tuberculous guinea pigs under conditions permitting the entrance of tubercle bacilli both by way of the alimentary and of the respiratory tracts, the type of lesion produced depends upon the relative intensity of exposure to infection by one or the other channel. With the gradual elimination of exposure to alimentary infection tuberculosis is more and more completely engrafted through the respiratory route. With the gradual increase in the intensity of exposure to alimentary infection, the disease becomes more and more completely enteric in origin. Some evidence is presented that the engrafting of tuberculosis by way of the alimentary route inhibits the development of respiratory disease.

A Study of Rural School Ventilation: The School Ventilation Study in Cattaraugus County, N. Y., 1926-27.—DUFFIELD (*Pub. Health Rep.*, 1929, **44**, 2383) states that there are in New York State about 8000 one- and two-room schools with about 150,000 pupils while in the whole country about 3,500,000 pupils attend such schools. The conclusions are as follows: (1) Rural schools heated by furnaces and jacketed stoves were more generally overheated than rooms with ordinary stoves. (2) Lateral temperature distribution was very good in the rooms heated by furnaces but very uneven in stove-heated schools. The average difference between temperatures on desk tops in different parts of the room exceeded 10° F. in nearly half the rooms, and in individual instances the observed difference was a great as 30° and 40° F. (3) Vertical differences in temperature were great, that is, floor temperatures were low—half the rooms averaging below 60° with one extreme record of 31°—and ceiling temperatures (in the rooms in which such observations were made) high—often over 90°, and in two rooms averaging over 100°—in rooms where no provision was made for the artificial circulation of air. (4) In general, one and two room rural schools, such as those observed in Cattaraugus County, appear to be highly unsatisfactory from the standpoint of heating and ventilation. They

are subject to gross overheating on the one hand and to serious chilling on the other, and show wide horizontal and vertical differences in the temperatures existing simultaneously in different parts of the same room. (During the Spring of 1928 three schools were provided with insulating material in varying degrees. The heating equipment in these and a few other schools was also replaced or altered and later it will be possible to report on the results that can be obtained under improved conditions in this type of school.) (5) Absenteeism in one- and two-room schools of Cattaraugus County ranged from 6 to 37.8 per cent, with an average of 14.1 per cent, which is twice as high as the average rates observed in Syracuse and New York City. The mean rates of the middle half of the rooms in the Cattaraugus County study fell between 10.7 and 17.5 per cent. (6) Absenteeism reported due to respiratory illness in the Cattaraugus County rural schools varied from 1.2 to 9.7 per cent of the total pupil sessions, with a mean of 4.7 per cent, which was twice as high as the corresponding rate for the current Syracuse study and four times that found in the New York City studies of the former commission. The middle half of the reported rates of respiratory illness absenteeism in the rural schools of Cattaraugus County fell between 2.3 and 6.4 per cent of the total pupil sessions. (7) In general, the prevalence of respiratory illness showed an inverse relationship to outdoor temperatures, that is, the incidence of respiratory illness was greater during the cold months of the year. In the absence of other factors, however, low temperature itself did not appear to be directly associated with increased respiratory illness. (8) During periods of low temperature, deviations from the general trend of the incidence of respiratory illness varied with the fluctuations in precipitation, the maximum effect occurring in the week following that which had an excess of precipitation, with the exception of the last week of the study.

Notice to Contributors.—Manuscripts intended for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence, should be sent to the Editor, DR. EDWARD B. KRUMBHAAR, School of Medicine, University of Pennsylvania, Philadelphia, Pa.

Articles are accepted for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively.

All manuscripts should be typewritten on one side of the paper only, and should be double spaced with liberal margins. The author's chief position and, when possible, the Department from which the work is produced should be indicated in the subtitle. Illustrations accompanying articles should be numbered and have captions bearing corresponding numbers. For identification they should also have the author's name written on the margin. The recommendations of the American Medical Association Style Book should be followed. It is important that references should be at the end of the article and should be complete, that is, author's name, title of article, journal, year, volume (in Arabic numbers) and page (beginning and ending).

Two hundred and fifty reprints are furnished gratis; additional reprints may be had in multiples of 250 at the expense of the author. They should be asked for when the galley proofs are returned.

Contributions in a foreign language, if found desirable for the JOURNAL, will be translated at its expense.